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Physical coronary arteriogenesis of cardiac and extracardiac origin

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Abstract

Coronary collaterals are pre-formed connections that provide an alternative route when regular antegrade blood flow to the heart muscle is compromised. In response to a coronary obstruction, coronary collaterals undergo gradual enlargement, variably compensating for impaired antegrade blood flow. As natural bypasses, sufficiently large coronary collaterals can preserve myocardial perfusion and viability in the acute and chronic phases of coronary artery disease.

In chronic stable coronary artery disease, medical therapy is complemented by established interventional therapies such as percutaneous coronary intervention and surgical coronary artery bypass grafting. However, new therapeutic options are needed for patients who are not candidates for conventional revascularization due to severe and/or diffuse obstructive coronary artery disease. Promotion of coronary collaterals represents such an alternative treatment option. However, while a multitude of interventions has been shown to be effective in collateral growth promotion, the effect of current interventions is only temporary and therefore recurrent application of the arteriogenic stimulus is necessary to sustain the level of collaterals. Historically, attempts to induce *durable* improvement of coronary collateral flow have already been made. Experimental and clinical studies examined the efficacy of distal ligation of the internal mammary artery (IMA) to augment blood flow to the coronary circulation. The basis of these studies was the clinical structural and experimental functional documentation of pre-formed connections between the internal mammary arteries and the coronary circulation - extracardiac collaterals. With the advent of coronary artery bypass grafting, the procedure was, however, abandoned. Notably, the clinical studies were based on crude outcome measures, such as symptomatic improvement. The *function* and in-vivo prevalence of inter-

nal mammary-to-coronary-anastomoses was therefore investigated in a clinical study (**Project I**) for the first time. 120 patients referred for elective coronary angiography for suspected or established coronary artery disease (CAD) underwent 180 pairs of coronary artery balloon occlusions, the first with and the second without simultaneous distal IMA occlusion (thought to augment flow via IMA-to-coronary connections). Collateral function was assessed during coronary balloon occlusion by collateral flow index (CFI), which is the ratio of coronary occlusive to aortic (effective perfusing) pressure, accounting for the back pressure (central venous pressure). Regional myocardial ischemia was assessed by the intracoronary electrocardiogram (ECG). With simultaneous distal IMA occlusion CFI was significantly higher during left IMA with left anterior descending coronary artery (LAD) occlusion and right IMA with right coronary artery (RCA) occlusion than during LAD or RCA occlusion alone. Conversely, during contralateral IMA occlusion, ie RCA with left IMA or LAD or left circumflex coronary artery (LCX) with right IMA occlusion, CFI was not different. Concordantly, myocardial ischemia by intracoronary ECG was lower during LAD or RCA occlusion with simultaneous ipsilateral IMA occlusion and was not different during contralateral IMA occlusion or with LCX occlusion. In conclusion, it could be demonstrated that there was functional, ischemia-reducing collateral supply from the ipsilateral IMA to the right coronary and the left anterior descending coronary artery.

The effect of permanent distal right IMA on coronary collateral function was investigated for the first time in an open-label clinical trial (**Project II**). 50 patients with stable CAD underwent distal right IMA closure at baseline and determination of right and left coronary function (LAD or LCX) by CFI at baseline and at follow-up 6 weeks after right IMA device closure. CFI in the untreated RCA increased significantly from baseline to follow-up, while CFI in the untreated left coronary remained unchanged. Concordantly, regional myocardial ischemia determined by intracoronary ECG was reduced during a 1-minute coronary balloon occlusion in the RCA but not in the left coronary. In conclusion, permanent distal right IMA closure in this non-randomized study appeared to augment extracardiac right coronary collateral supply.

With acute myocardial ischemia, the mainstay of therapy lies in the antegrade technique of prompt percutaneous revascularization. However, a reopened epicardial conduit artery does not guarantee reperfusion of myocardial tissue, which can be

impaired by microvascular dysfunction. In this situation of a failed antegrade approach, retrograde treatment approach has been proposed by an intervention in the coronary venous system - intermittent coronary sinus occlusion (CSO). Although the ischemia-relieving effect of CSO is thought to depend on coronary collaterals, its role of coronary collaterals has so far not been clearly defined in humans.

The role of coronary collaterals in the anti-ischemic effect of CSO was therefore investigated in a clinical study (**Project III**) and in a computer simulation (**Project IV**). In the clinical study, 35 patients with stable coronary artery disease underwent two 2-minute balloon occlusions of a major coronary artery to induce controlled ischemia. CSO was performed randomized to the first or second coronary balloon occlusion. Collateral function was assessed by CFI and regional myocardial ischemia was assessed by the ST-segment shift in the intracoronary ECG. Intermittent coronary sinus occlusion was shown to reduce myocardial ischemia depending on the extent of collateral function. With minimal collateral function, no ischemia-reducing effect of CSO was demonstrated. An anti-ischemic effect of CSO was seen with intermediate collateral function. High collateral function prevented myocardial ischemia in the first place and therefore, no additional effect of CSO was demonstrated.

The computer simulation (**Project IV**) consisted of a lumped-parameter model of a two-branch left coronary system circuit with arterial, capillary and venous compartments. As a key point, arterial collateral connections were an integral part of the model, in contrast to prior computer models. Importantly, the salient features of coronary pressure and flow during non-ischemic and ischemic conditions, as well as during CSO could be reproduced. In particular, the proposed main mechanism of CSO - retrograde flow from the venous to the venular and capillary compartment was reproduced by the model. As a key point, the model predicted retrograde flow to be dependent on the extent of collateral blood flow and contractility. With minimal collateral function, retrograde flow to an ischemic region was low, while it progressively increased with higher collateral function. Accounting for the combination of reduced contractility during ischemia and the level of collateral function, the effect on retrograde flow was much increased. Retrograde flow was predicted to be very low at zero to minimal collateral function and concomitantly severely reduced contractility. Conversely, retrograde flow increased steeply with increasing collateral function and more preserved contractility. In essence, the mathematical model provided a reasonable explanation for the findings from the clinical study (Project III)

and could, for the first time, provide an explanation for the role of collaterals in the anti-ischemic effect of CSO.

Abbreviations

- CABG** coronary artery bypass grafting.
- CAD** coronary artery disease.
- CEP** cavity-induced extracellular pressure.
- CFI** collateral flow index.
- CS** coronary sinus.
- CSI** coronary sinus intervention.
- CSO** coronary sinus occlusion.
- CSP** coronary sinus pressure.
- CTO** chronic total occlusion.
- ECG** electrocardiogram.
- ECP** extravascular compressive pressure.
- ICSO** intermittent coronary sinus occlusion.
- IMA** internal mammary artery.
- L1** first left coronary branch.
- L2** second left coronary branch.
- LAD** left anterior descending coronary artery.
- LCX** left circumflex coronary artery.

LPM lumped parameter model.

LV left ventricle.

LVP left ventricular pressure.

MI myocardial infarction.

p_{ao} aortic pressure.

p_{RA} right atrial pressure.

PCI percutaneous coronary intervention.

PIV posterior interventricular vein.

RC Resistor-Capacitor.

RCA right coronary artery.

STEMI ST-segment elevation myocardial infarction.

1. Introduction

1.1 Impact of the Coronary Collateral Circulation in Coronary Artery Disease

Despite considerable advances in medicine, cardiovascular diseases remain the number one cause of death globally - primarily as a consequence of myocardial infarction due to acute coronary occlusion. Compromise of blood flow is, however, lessened by coronary collaterals, which provide an alternative source of blood flow to myocardium jeopardized by ischemia. Coronary collaterals represent pre-existing inter-arterial anastomoses and as such are the natural counter-part of surgically created bypasses. The extent of coronary collaterals has been shown to vary widely between individuals, both in the absence and in the presence of coronary narrowings.[1] When sufficient, coronary collaterals have been shown to confer a significant benefit in terms of overall mortality and cardiovascular events.[2, 3]

Current treatment modalities for CAD comprise medical treatment and revascularization, either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Although widely used, PCI has not been shown to reduce the incidence of myocardial infarction or death in patients with stable CAD compared to medical therapy. In contrast, CABG significantly reduced rates of death and myocardial infarction compared to PCI. Conceptually, the advantage of CABG over PCI with more severe CAD relates to the protective effect of bypasses, providing an alternative source of blood flow in the event of coronary occlusion. Similarly, coronary collaterals serve as natural as opposed to artificial surgical bypasses.

In this regard, the concept of augmenting coronary collateral function as an alternative treatment strategy to alter the course of CAD, as well as to control symptoms,

is attractive.

A multitude of interventions has been shown to be efficacious in collateral growth promotion. Apart from delivery of arteriogenic agents,[4, 5, 6, 7, 8] several means for physical collateral growth promotion have been shown to be effective.[9, 10, 11, 12, 13] However, so far, the effect of current interventions of both these modalities is only temporary and therefore recurrent application of the arteriogenic stimulus is necessary to sustain the level of collaterals. Notwithstanding, there have been historical attempts to induce durable improvement of coronary collateral flow.

1.2 Extracardiac Collaterals

Colloquially, coronary collaterals are synonymously used with the term intracardiac coronary collaterals, ie they are implicitly understood to originate from and connect to coronary arteries. However, pathological and experimental studies have confirmed the existence of collaterals connecting the coronary circulation with an extracardiac vessel - *extracardiac* collaterals.[14, 15, 16]

In contrast to the extensively studied coronary collateral circulation within the heart,[17, 18] limited data exist on extracardiac-to-coronary anastomoses.[16] Furthermore, existing data rely on visual methods insensitive for the adequate detection of structurally present but poorly functional anastomoses. Most of the knowledge comes from pathological studies, which are summarized in Table 1.1. The first demonstration of anastomoses between coronary arteries and mediastinal vessels was by von Haller in 1803.[19]

A potential merit for further investigation are the prior clinical data supporting a role for extracardiac anastomoses as a target for durable promotion of coronary collateral function. Such a therapeutic approach appears especially attractive with regard to connections between the IMA and the coronary circulation, which have been documented macroscopically in one tenth of patients with CAD.[20]

1.2.1 Anatomical Background

In the absence of pericardial adhesions, blood supply from extracardiac collaterals to the heart is possible via the pericardial reflections, located posterior to the heart between the roots of the great vessels.[20] This is consistent with Hudson, who reported the most extensive anastomoses between cardiac and extracardiac vessels to

be around the ostia of the pulmonary veins.[15] The (parietal) pericardium receives blood supply from the IMAs (via the pericardiophrenic arteries) and the bronchial arteries (to the posterior part of the pericardium).[21] Given their proximity to the pericardial reflections, either the IMAs or the bronchial arteries therefore usually give rise to extracardiac coronary collaterals.[14, 22, 20]

Apart from the vasa vasorum of the aorta, a possible pathway between the IMA or the bronchial artery and the coronary circulation is represented by the atrial coronary branches (Figure 1.1).[20, 14] While the atrial coronary branches show high anatomical variability, the most constant (and largest) atrial branches are those supplying the sinus node and atrioventricular node, respectively.[23] Regularly the largest atrial coronary branch, the sinus node artery arises slightly more frequently from the RCA than the from the LCX, usually within its first few centimeters. The atrioventricular node artery, typically smaller than the sinus node artery, originates from the RCA in the majority of cases.[23] Numerous, but smaller and variable atrial branches can be designated simply as right (from RCA) or left atrial arteries (from LCX).

On anatomical grounds, atrial coronary branches would conceivably mediate an extracardiac connection to the coronary artery it originates from, e.g. a sinus node coronary artery arising from the right coronary artery would therefore provide a potential route for an extracardiac source to the right coronary artery. However, grossly visible anastomoses exist between the atrial coronary branches of the right and left coronary arteries, implying a potential route for direct communication between the right and left coronary arteries.[24] As a corollary, an extracardiac connection mediated by a particular atrial branch would also be conceivable to communicate with a major coronary branch via atrial anastomoses irrespective of the origin of the mediating atrial branch.

1.2.2 Internal Mammary Artery-to-Coronary Collaterals

With respect to a therapeutic intervention aiming at promotion of extracardiac anastomoses, the connections from the internal mammary arteries have become the subject of interest.

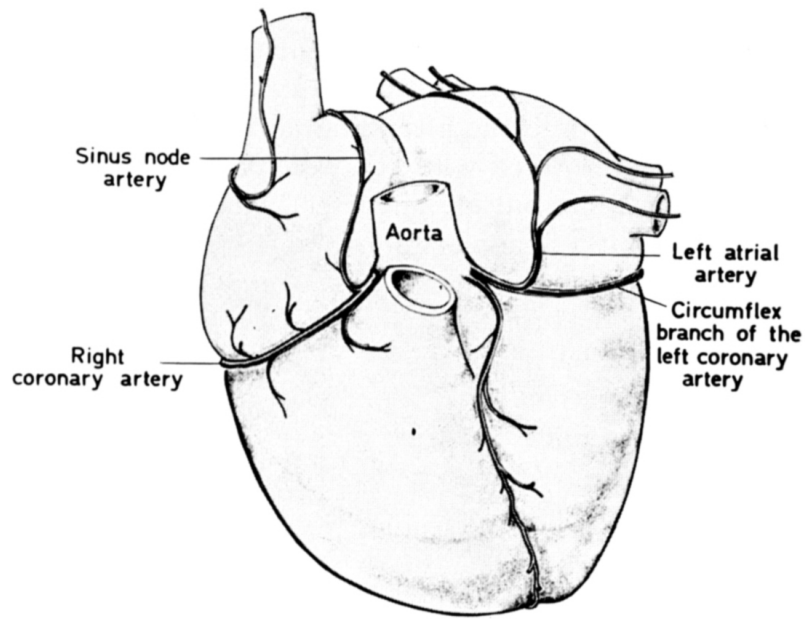


Figure 1.1: Atrial coronary branches

Source: [14]

Anatomical background

The IMA of both sides originate proximally from the subclavian artery and run caudally within a few centimeters laterally of the sternum. At the sixth-to-seventh intercostal space they divide into their terminal branches, the musculophrenic artery (laterally) and superior epigastric artery (medially). The superior epigastric artery, in turn, anastomoses with the inferior epigastric artery, which arises from the external iliac artery.

With respect to an extracardiac connection to the coronary circulation, the most important branch of the IMA is the pericardiophrenic artery, which branches off the IMA near its upper end and runs with the phrenic nerve to reach the diaphragm. The pericardiophrenic artery provides blood supply to the parietal pericardium, which highlights its potential to form anastomoses with the coronary circulation via the pericardial reflection. Other arteries supplying the pericardium are pericardial branches from bronchial, esophageal or superior phrenic arteries.

Author	Origin of extracardiac collateral	Frequency
Moberg 1967	IMA	19/49 (38.8%)
Moberg 1967	bronchial arteries	45/45 (100%)
Björk 1967	bronchial arteries	73/200 (36.5%)
Hudson 1932	branches of aorta (incl. bronchial arteries), IMA (via pericardio-phrenic branches)	NA

Table 1.1: Post-mortem angiography studies on extracardiac coronary collaterals.
IMA, internal mammary artery.

Post-mortem angiography studies

The only detailed and comprehensive study regarding IMA-to-coronary anastomoses is the one by Moberg, who also examined bronchial-to-coronary anastomoses.[20, 14] Post-mortem, contrast agent was injected directly into the right IMA with the exception of two patients, where contrast injection was performed into the left IMA. Contrast filling of the IMA contralateral to the injected one was deemed to occur sufficiently through inter-IMA-anastomoses (via retrosternal branches).[25] Radiograms were then assessed for contrast filling in the coronary arteries on atrial or ventricular level. A total of 49 subjects were investigated, in none of which pericardial adhesions were observed, therefore excluding the possibility of extracardiac anastomoses to be facilitated by this condition.[26, 27] By this angiographic method, an extracardiac, IMA-to-coronary anastomoses could be documented in 19 (38.8%) of patients. Table 1.2 gives the details of his study.

Subjects - n (%)	Terminal coronary branch filled	Connecting branch
15/49 (30.6)	atrial coronary branch	NA
4/49 (8.2)	ventricular branch	
	RCA (1 case)	sinus node artery
	LCX (3 cases)	left atrial artery

Table 1.2: Post-mortem angiography study on IMA-to-coronary anastomoses.
LAD, left anterior descending. LCX, left circumflex. RCA, right coronary artery.

Source: [20]

Angiographic case reports

In-vivo, the structural existence of IMA-to-coronary artery connections has rarely been demonstrated, exclusively in the context of coronary angiography for the evaluation of CAD. Table 1.3 gives an overview of the angiographic case reports on IMA-to-coronary connections. A constant in these cases was severe obstruction of the collateral-receiving coronary artery. In contrast to the post-mortem study by Moberg, the in-vivo angiographic cases allow to evaluate from which side of the IMA the extracardiac collateral originates from. With one exception, the anastomoses between the IMA and the coronary circulation were documented to be ipsilateral, ie, left IMA to a branch of the left coronary artery (LCX or LAD), or right IMA to RCA. In 2 of the cases, a prior CABG had been performed, which may have enabled the development of the observed connection to have occurred by transpericardial vascularization secondary to pericardial adhesions.[26]

Origin	Coronary	Connecting branch	Prior heart surgery	Reference
LIMA	LAD	pericardial branch	yes, saphenous vein bypass grafting	Salachas [28]
	LAD	NA	yes, coronary artery bypass grafting	Knight [29]
	LAD	NA	yes, coronary artery bypass grafting, aneurysmectomy	Aras [30]
LIMA	LCX	pericardial branch, left atrial branch	no	Yamamoto [31]
RIMA	RCA	pericardial branch, sinus node artery	no	Singh [32]
	RCA	pericardial branch, sinus node artery	no	Kajinami [33]
RIMA	LCX	pericardial branch	no	Numata [34]

Table 1.3: Angiographic case reports of natural IMA-to-coronary anastomoses.

LAD, left anterior descending. LCX, left circumflex. LIMA, left internal mammary artery. RCA, right coronary artery. RIMA, right internal mammary artery.

Promotion of IMA-to-coronary collaterals

Before the advent of CABG, several experimental and clinical studies set out to investigate the promotion of coronary collateral flow via IMA-to-coronary anastomoses. In the majority of cases, ligation of the IMA distal to the take-off of the presumptive donor branch (the pericardiophrenic branch) was performed, with the idea to redirect blood flow and thus enhance the naturally pre-existing anastomoses.

Experimental studies

Table 1.4 summarizes the major experimental studies investigating the efficacy to promote IMA-to-coronary flow. With the exception of a subgroup in Chatterjee's study,[35] IMA ligation distal to the pericardiophrenic branch was performed as a means of IMA-to-coronary collateral promotion. Mostly, mortality was assessed, which has to be regarded as an insensitive endpoint in light of several methodical shortcomings.

Instructive to the interpretation of the data are the studies by Blair[36, 37] and a substudy by Bogedain.[38] Both assessed the effect of *acute* IMA ligation on coronary blood flow, albeit by different methods. In response, a small, but consistent increase in coronary blood flow was found. Furthermore, Blair et al. found that the observed increase was reversed by clamping of the IMA at their origin. Collectively, therefore, these studies provide a proof of principle for IMA ligation as a means to promote extracardiac collateral function.

In contrast to other investigations related to (intracardiac) collaterals, a constant of the experimental studies on extracardiac collateral promotion was that coronary occlusion was always acute. However, a sizeable enlargement of any collateral connection in response to coronary constriction takes (days to) weeks. Consequently, any additional blood flow by IMA-to-coronary anastomoses was likely small given that enlargement of pre-existing, but minute extracardiac connections could not occur. In some of the studies, there was a time interval between ligation of the IMA and the coronary artery, which may have lead to an enlargement of the pre-existing anastomoses. However, a potential arteriogenic effect of IMA ligation was likely to be small in the absence of a significant pressure gradient between the donor (IMA) and the recipient artery, such as would have been the case with severe coronary narrowing. Taken together, the experimental findings are consistent with the proof

of principle that IMA ligation can additionally contribute to augment extracardiac coronary collateral flow, but that its recruitable extent is ineffective in reducing mortality secondary to acute coronary occlusion in the absence of additional promoting factors (i.e. a coronary narrowing).

Author	IMA Intervention	Coronary Intervention	Result
Blair 1957 [36]	IMA ligation, bilateral	none	increase in coronary flow (avg 9.6 ml/min)
Blair 1960 [37]	IMA ligation, bilateral	none	increase in coronary flow (avg 7.3 ml/min)
Glover 1957 [39]	treatment: IMA ligation, bilateral	coronary ligation	93% mortality
	control: none	coronary ligation	42% mortality
Chatterjee 1963 [35]	IMA ligation, bilateral	LAD ligation, acute	100% mortality
	IMA arteriovenous shunt, bilateral	LAD ligation, acute	16.7% mortality
Vansant 1959 [40]	control: none	LAD ligation, acute	90% mortality, 60% with irreversible ventricular fibrillation
	IMA ligation, bilateral	LAD ligation, acute	70% mortality, 50% with irreversible
	IMA ligation, bilateral	LAD ligation, 2 weeks after IMA ligation	ventricular fibrillation, infarct size not different
Katznelson 1960 [41]	control: none	none	no radiographic evidence of anastomoses between pericardiophrenic and coronary arteries
	IMA ligation, bilateral	none	

Author	IMA Intervention	Coronary Intervention	Result
Rueger 1960 [42]	IMA ligation, bilateral, pleural cavity left closed	LAD ligation, 3 weeks after IMA ligation	27% mortality
	IMA ligation, bilateral, pleural cavity opened	LAD ligation, 3 weeks after IMA ligation	30% mortality
	none: sham IMA ligation	LAD ligation, 3 weeks after sham IMA ligation	40% mortality
	none: anesthesia	LAD ligation, 3 weeks after anesthesia	40% mortality
	none	LAD ligation, acute	55% mortality
	IMA ligation, bilateral	LAD ligation, acute	70% mortality
Sabiston 1958 [43]	IMA ligation, bilateral	LAD ligation, acute	78% mortality
	IMA ligation, bilateral; ligation of the other branches of the subclavian artery	LAD ligation, 33 days after IMA ligation	93% mortality
	IMA ligation, left; ligation of the other branches of the subclavian artery	LAD ligation, 46 days after IMA ligation	92% mortality

Author	IMA Intervention	Coronary Intervention	Result
Bogedain 1962 [38]	control: none	LAD ligation, acute	78% mortality
		LCX ligation, acute	100% mortality
		LAD and LCX ligation, acute	67% mortality
	IMA ligation, bilateral	LAD ligation, 3 weeks after IMA ligation	25% mortality
		LCX ligation, 3 weeks after IMA ligation	67% mortality
		LAD and LCX ligation, 3 weeks after IMA ligation	100% mortality
	IMA ligation, bilateral	none	15% increase in coronary flow

Table 1.4: Major experimental studies on promotion of IMA-to-coronary anastomoses

IMA, internal mammary artery. LAD, left anterior descending. LCX, left circumflex.

Clinical studies

Based on anatomical considerations, bilateral IMA ligation was first proposed by the Italian surgeon Fieschi and the first clinical case was performed in in 1939.[44] The procedure could be performed under local anesthesia via a small incision in an intercostal space. Two major clinical, but uncontrolled studies in several hundreds of patients showed subjective improvement in symptoms in most patients after the procedure, while objective measures by electrocardiography were observed to a lesser extent.[45, 46] However, two randomized, controlled trials showed similar improvement in symptoms in the group undergoing the sham procedure.[47, 48] Notably, a major limitation of both randomized studies was the small sample size (17 and 18 patients, respectively). Nevertheless, with the introduction of the cardiopulmonary bypass technique enabling CABG, the procedure was abandoned.

1.3 Coronary Sinus Interventions

Coronary *artery* reperfusion is the mainstay of therapy in acute myocardial ischemia. Persisting myocardial ischemia can, however, occur even after desobstruction of the culprit epicardial conduit artery, as effective reperfusion of myocardial tissue depends also on the coronary microvasculature, the function of which can be impaired especially after prolonged ischemia. Myocardial tissue hypoperfusion that persists despite a reopened conduit artery is known as the no-reflow phenomenon, the cause of which has been attributed to a dysfunction of the coronary microcirculation. Clinically, the no-reflow phenomenon is relevant due to its being a strong predictor for long-term mortality in patients with acute myocardial infarction.

Current treatment approaches for no-reflow have so far been disappointing and highlight the need for alternative management strategies. As an alternative to the conventional antegrade approach, a retrograde approach has been investigated in clinical and experimental studies of acute myocardial ischemia. Conceptually, the retrograde approach, also termed retroperfusion, relates to manipulation of the coronary venous system to improve regional myocardial blood flow in ischemic territories. The technique has found a regular application in retrograde cardioplegia during cardiopulmonary bypass, where distribution of the cardioplegic solution can be impaired in the setting of severe CAD when infused by the antegrade approach.[49] In acute coronary syndrome, its use is investigated as an adjunct to PCI, whereas in chronic stable CAD, it is investigated as an alternate therapy for patients with refractory angina who are not candidates for conventional revascularization procedures.[50, 51, 52] Regardless of the employed retroperfusion method, a reduction in myocardial infarct size has been observed after coronary occlusion in experimental models compared to a control group.[53]

Several mechanisms have been proposed to underlie the anti-ischemic effect of coronary sinus pressure elevation. While the concept of effective retrograde perfusion from the coronary veins to the ischemic region is appealing, several considerations have to be taken into account. In particular, this relates to the coronary venous anatomy and the role of coronary collaterals, which has not been investigated so far in humans.

With regard to the acute application of retrograde perfusion methods in acute my-

ocardial ischemia, the observed hemodynamic reactions reflect functional changes of the coronary arterial and venous system. Conversely, a structural adaptation could be imagined with chronic elevation of coronary sinus pressure. In this respect, a clinical study has recently investigated the safety and efficacy of a coronary sinus reducer stent in patients with chronic refractory angina pectoris not amenable to conventional therapy.

1.3.1 Coronary Venous Anatomy

The efficacy of coronary venous intervention to result in effective retroperfusion is critically determined by the anatomy of the coronary network, in particular the cardiac venous anatomy (Figure 1.2). [54] Two major distinct drainage pathways for coronary flow exist. The majority of coronary flow returns via large epicardial veins to the right atrium, most of them via the coronary sinus (CS), while some veins open directly into the right atrium.[55] These connections are known as the greater (major) cardiac venous drainage system. Conversely, the thebesian vessels (or smaller (minor) cardiac drainage system) are small vessels originating from the subendocardial region and connecting directly to the ventricular cavities.

Myocardium drained by non-coronary sinus pathways

It is reasonable that CSO may not reperfuse myocardium draining by pathways other than the CS. Non-coronary sinus drainage is the rule for the myocardium of the right ventricle, which is illustrated by its ineffective perfusion by retrograde cardioplegia via the CS.[57, 58]. Most of the right ventricle is perfused by the RCA. With respect to the left ventricle (LV), the RCA perfuses the inferior and infero-posterior territory (with right coronary dominance, which is the usual case). The major cardiac vein draining the part of the LV supplied by the RCA is the posterior interventricular vein (PIV), also known as the middle cardiac vein.[59] While the PIV opens into the CS in the majority of cases, it does so typically near its end. Placement of the occluding balloon is therefore likely to exclude the PIV due to its more proximal placement in the CS. On anatomical grounds and experimental observations, CSO is therefore ineffective in the case of RCA ischemia.

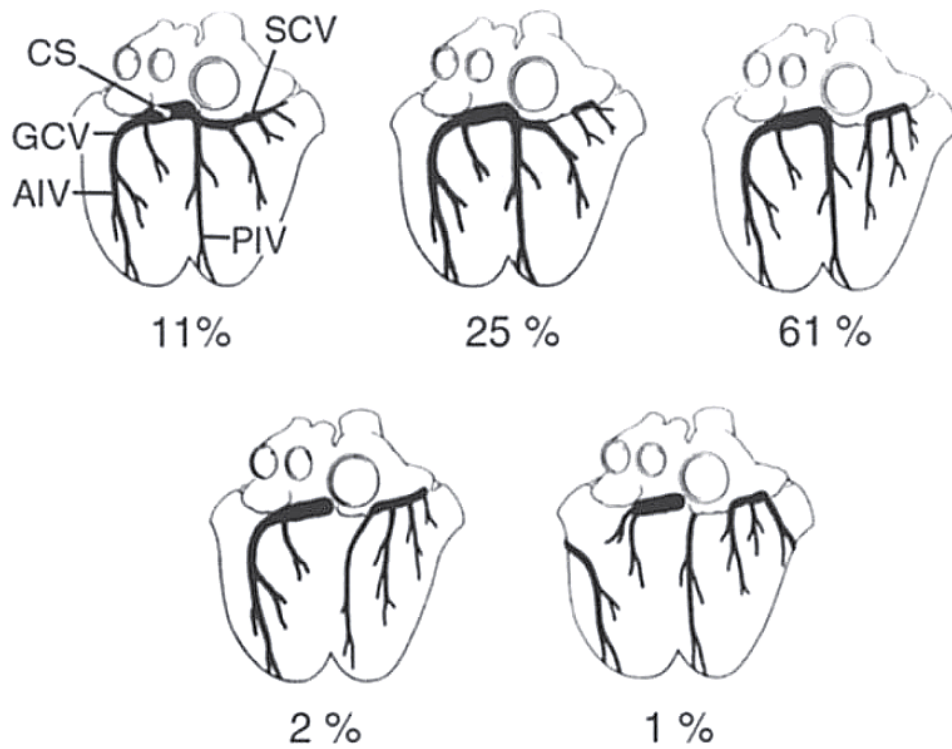


Figure 1.2: Distribution patterns of the major cardiac veins and their mode of termination.

AIV, anterior interventricular vein; CS, coronary sinus. GCV, great cardiac vein. PIV, posterior interventricular vein. SCV, small cardiac vein.

Source: [56]

1.3.2 Hemodynamic Effects of (Intermittent) Coronary Sinus Occlusion

Elevation of coronary sinus pressure

CSO is typically performed by inflating a balloon in the coronary sinus. Occlusion is released periodically, as permanent occlusion would result in myocardial injury.[60] Coronary sinus pressure (CSP) increases with CSO with a typical pattern, (Figure 1.3).

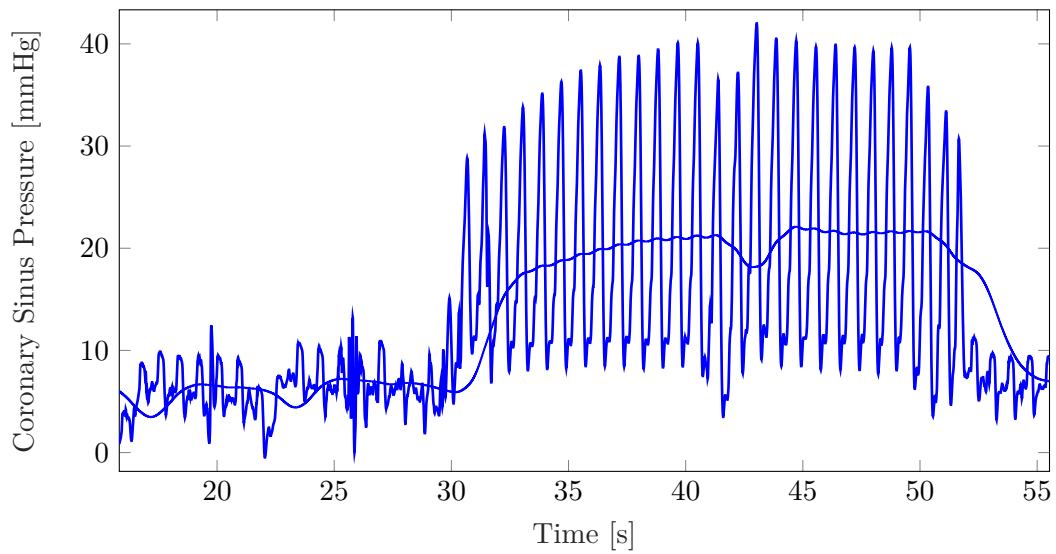


Figure 1.3: Typical pattern of coronary sinus pressure during coronary sinus occlusion (starting at 30 seconds). Recording from a patient from a clinical study.[61]

Coronary inflow reduction

If the coronary circulation were a single-route system, blockage of the outflow would eventually result in total cessation of antegrade blood flow. However, drainage of myocardium occurs not only via the coronary sinus, but also via the thebesian vein system from the subendocardial region to the ventricular cavities and via smaller collecting epicardial veins directly to the right atrium. The extent of these alternative drainage pathways therefore dictate the effective resistance to inflow. The findings from experimental studies are consistent with these considerations.

Right coronary inflow is principally unaltered during CSO, owing to its predominant drainage directly to the right atrium.[62, 63, 64] With respect to left coronary inflow, a reduction has been observed in experimental studies during CSO in dogs.[62, 65, 66, 64] Elevation of the CSP did, however not significantly influence left coronary inflow in sheep.[67] The differential effect is likely explained by the greater extent of draining pathways alternative to the CS, especially the thebesian vein system. In other words, a greater extent of left coronary drainage via thebesian connections in sheep provides an explanation for the lack in inflow reduction during CSP elevation.

Redistribution of venous outflow

With increasing CSP, CS outflow is redistributed to alternative draining pathways.[68] On an anatomical basis, these are principally the thebesian vessels draining to the ventricular chambers and the anterior cardiac veins draining directly to the right atrium. The anterior cardiac veins provide an alternative drainage pathway by virtue of its frequent communication with the coronary sinus vessel, representing epicardial veno-venous connections.[69]

1.3.3 Influence of Coronary Collaterals on Intermittent Coronary Sinus Occlusion

The extent of collaterals per se is an important determinant of the magnitude of ischemia in a dependent myocardial region.[70, 71] If well-developed, coronary collaterals not only lessen but prevent myocardial ischemia at rest and even during exercise.[72] In animals, the extent of coronary collaterals varies significantly between species.[73, 74] Pigs[75] and sheep[76] have a minimal collateral circulation, while dogs[77] show relatively well-developed coronary collaterals. Experimental studies on CSO have been conducted in different species, which permits to gain insight of the role of coronary collaterals in the anti-ischemic effect of CSO.

A compelling argument for the role of coronary collaterals would be the demonstration of increased myocardial salvage by CSO in species with well-developed collaterals relative to control, as compared to species with poor collaterals. Such a comparison is, however, precluded by the heterogenous study protocols employed even within the same type of coronary sinus intervention.[53] In other words, differences in myocardial salvage could be attributed to a particular study protocol, rather than to a

differential effect mediated by the extent of collateral connections.

In an experimental study in dogs, regional myocardial blood flow in the ischemic region produced by coronary occlusion increased in response to CSO.[78] Mean collateral flow was 25% of normal in this experiment. It was hypothesized that CSO would increase outflow resistance (via an increase in CSP) in the collateral-donor vessel, thereby mediating a flow diversion through the collateral channels. Regional myocardial blood flow was more increased with higher CSP, consistent with the notion of increased flow diversion via collaterals by increased outflow impedance in the collateral donor. Conversely, in an animal model without significant collateral circulation (in pigs), CSO did not improve regional myocardial blood flow or mechanical function of the ischemic bed induced by acute coronary occlusion.[79]

Another argument in favour of a mediating role of coronary collaterals in the anti-ischemic effect of CSO can be gained by comparing its effect to selective coronary vein occlusion. While with CSO, sizeable reductions in myocardial infarction (MI) size compared to control were observed in dogs,[80, 81, 82] selective vein occlusion did not reduce MI size.[83] Selective occlusion of the vein draining the ischemic region does not lead to outflow impedance in a collateral donor vessel, in contrast to occlusion of the large collecting vein such as the coronary sinus vessel, which might serve as a possible explanation for the disparate findings.

Of note, regional myocardial blood flow in the above mentioned studies was invariably measured by the microsphere method. The microsphere technique is suitable for measurement of collateral blood flow, but fails to detect retrograde blood flow from the venous system.[84, 85] The reduction of MI size by CSO in animals with minimal collateral circulation[86, 87, 88] and in the absence of an increase in (antegrade) myocardial blood flow might therefore be explained by effective retrograde blood flow from the venous compartment.

Given the multiple variables implicated in the effect of CSO, a computer simulation presents a possibility to estimate the influence of each factor independently.

2. Hypotheses and Aims of the Thesis

Project I

Objective: To determine of the in vivo prevalence and functional distribution of natural internal-mammary to coronary artery connections.

Hypothesis: Natural internal-mammary to coronary artery connections are functionally prevalent in a majority of patients.

Project II

Objective: To determine the safety and efficacy of permanent right distal internal mammary occlusion on coronary collateral function.

Hypothesis: Permanent right distal internal mammary artery closure is safe and effective in promoting right coronary collateral function.

Project III

Objective: To determine the influence of coronary collaterals on the effect of intermittent coronary sinus occlusion on acute myocardial ischemia in humans.

Hypothesis: the effect of intermittent coronary sinus occlusion on acute myocardial ischemia is modulated by the extent of the collateral circulation.

Project IV

Objective: To develop a lumped parameter mathematical model of the hemodynamic reactions of intermittent coronary sinus occlusion during acute coronary occlusion, with a special regard of the influence of coronary collaterals.

Hypothesis: The direct or indirect influence of coronary collaterals can be elucidated in a mathematical model.

3. Results

3.1 Project I

Function of Natural Internal Mammary-to-Coronary Artery Bypasses and Its Effect on Myocardial Ischemia

The first project aimed at determining the functional prevalence of natural bypasses between the internal mammary arteries and the coronary circulation and its ischemia-abating effect in humans.

My contributions were the conception and design of the project, acquiring, analyzing and interpreting the data, assisting in statistical analysis, handling funding of the project and making critical revision of the manuscript for important intellectual content.

The paper was published in *Circulation* in June 2014, journal ranking was #2 according to impact factor and #2 according to SCImago Journal Rank (SJR)[89] in the year of publication in Cardiology and Cardiovascular Medicine.

Function of Natural Internal Mammary-to-Coronary Artery Bypasses and Its Effect on Myocardial Ischemia

Michael Stoller, Stefano F. de Marchi and Christian Seiler

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Function of Natural Internal Mammary-to-Coronary Artery Bypasses and Its Effect on Myocardial Ischemia

Michael Stoller, MD; Stefano F. de Marchi, MD; Christian Seiler, MD

Background—The function of naturally existing internal mammary (IMA)-to-coronary artery bypasses and their quantitative effect on myocardial ischemia are unknown.

Methods and Results—The primary end point of this study was collateral flow index (CFI) obtained during two 1-minute coronary artery balloon occlusions, the first with and the second without simultaneous distal IMA occlusion. The secondary study end point was the quantitatively determined intracoronary ECG ST-segment elevation. CFI is the ratio of simultaneously recorded mean coronary occlusive pressure divided by mean aortic pressure both subtracted by mean central venous pressure. A total of 180 pairs of CFI measurements were performed among 120 patients. With and without IMA occlusion, CFI was 0.110 ± 0.074 and 0.096 ± 0.072 , respectively ($P < 0.0001$). The difference of CFI obtained in the presence minus CFI obtained in the absence of IMA occlusion was highest and most consistently positive during left IMA with left anterior descending artery occlusion and during right IMA with right coronary artery occlusion (ipsilateral occlusions): 0.033 ± 0.044 and 0.025 ± 0.027 , respectively. This CFI difference was absent during right IMA with left anterior descending artery occlusion and during left IMA with right coronary artery occlusion (contralateral occlusions): -0.007 ± 0.034 and 0.001 ± 0.023 , respectively ($P = 0.0002$ versus ipsilateral occlusions). The respective CFI differences during either IMA with left circumflex artery occlusion were inconsistently positive. Intracoronary ECG ST-segment elevations were significantly reduced during ipsilateral IMA occlusions but not during contralateral or left circumflex artery occlusions.

Conclusion—There is a functional, ischemia-reducing extracardiac coronary artery supply via ipsilateral but not via contralateral natural IMA bypasses.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01676207.

(*Circulation*. 2014;129:2645-2652.)

Key Words: collateral circulation ■ coronary circulation ■ mammary arteries ■ thoracic arteries

In patients with chronic coronary artery disease (CAD), prognosis is adversely affected by ischemia.¹ Likewise, the extent of ischemia and necrosis is the main determinant of outcome after acute myocardial infarction.² Both the degree of myocardial ischemia and the resulting infarct size can be estimated by ECG ST-segment shift, in particular and very sensitively by intracoronary ECG.^{3,4} The absence of intracoronary ECG ST-segment shift during a brief coronary balloon occlusion has been demonstrated to be a beneficial prognosticator of survival.⁵ Myocardial ischemia in the event of coronary occlusion is influenced by the duration of occlusion, the size of the myocardial area at risk for infarction, the lack of collateral supply to the ischemic zone, the absence of ischemic preconditioning before vascular occlusion, and the level of myocardial oxygen consumption at the time of occlusion.⁶ The beneficial effect on survival of a well-functioning intercoronary collateral circulation in chronic stable CAD has been well documented.⁷⁻⁹

Clinical Perspective on p 2652

Anatomically, extracardiac coronary collateral supply via internal mammary artery (IMA) branches to the pericardium was described >80 years ago.^{10,11} In the advent of coronary bypass surgery, bilateral IMA ligation in patients with CAD

has been suggested to alleviate angina pectoris and ECG signs of ischemia,¹²⁻¹⁶ although this finding has been challenged by 2 very small sham-controlled trials.^{17,18} Using angiographic techniques, a total of 3 case reports have described the structural existence of in vivo naturally occurring anastomoses between one of the IMAs and the coronary circulation.¹⁹⁻²¹ Very recently, an experimental study in 8 dogs undergoing coronary artery constriction and IMA ligation failed to reveal myocardial microsphere perfusion via IMA in the single animal that survived the entire study protocol.²²

Hence, the prevalence, functional relevance, and effect on myocardial ischemia of extracardiac coronary collateral supply via natural IMA bypasses are unknown. The present study in patients without and with CAD tested the hypotheses that coronary collateral function increases in the presence versus the absence of distal IMA balloon occlusion and that the former is reflected by reduced myocardial ischemia.

Methods

Study Design and Patients

This was a prospective, observational study in 120 patients undergoing coronary angiography for diagnostic purposes in the context of chest pain. The primary study end point was collateral flow index (CFI; see

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below for calculation) obtained in 180 instances during two 1-minute coronary artery balloon occlusions (a total of 360 measurements), the first with and the second without simultaneous distal IMA balloon occlusion (Figure 1). Half of the patients with half of the measurements underwent assessment of ipsilateral IMA-to-coronary artery anastomoses (left IMA to left coronary artery and right IMA to right coronary artery), and half of the patients with half of the measurements underwent assessment of contralateral IMA-to-coronary artery anastomoses. Secondary study end points were the quantitatively determined intracoronary ECG ST-segment elevation and angina pectoris during the same 1-minute coronary occlusions. Criteria for study inclusion were age >18 years, written informed consent to participate in the study, and 0- to 3-vessel chronic stable CAD. Exclusion criteria were acute coronary syndrome, previous myocardial infarction in the vascular region undergoing CFI measurement, and severe hepatic or renal failure (creatinine clearance <15 mL·min⁻¹·1.73 m⁻²).

The study was approved by the ethics committee of the Kanton of Bern, Switzerland, and all patients gave written informed consent to participate.

Cardiac Catheterization and Coronary Angiography

Patients underwent left heart catheterization and coronary angiography for diagnostic purposes from the right femoral artery approach. Biplane left ventriculography was performed, followed by coronary angiography. Coronary artery stenoses were determined quantitatively as percent diameter reduction with the guiding catheter used for calibration. Aortic pressure (P_{ao}) was obtained with a 6F coronary artery guiding catheter. Central venous pressure (CVP) was measured via the right femoral vein.

Invasive Coronary Assessment

Primary Study End Points

Coronary occlusive collateral flow relative to normal antegrade flow through the nonoccluded coronary artery (CFI) was determined from coronary pressure measurements. A 0.014-in pressure-monitoring angioplasty guide wire (Pressure Wire, St. Jude Medical, Eschborn, Germany) was set at zero, calibrated, advanced through the guiding catheter, and positioned in the distal part of the vessel of interest. CFI was determined by simultaneous measurement of mean P_{ao} (mmHg), the distal coronary artery pressure during balloon occlusion (P_{occl} ; mmHg), and the CVP (mmHg; Figure 2) obtained during the last 30 seconds of the 1-minute coronary balloon occlusions. CFI was calculated as (P_{occl} –CVP) divided by (P_{ao} –CVP).²³ The accuracy of pressure-derived CFI measurements compared with ECG signs of myocardial ischemia during occlusion and with absolute myocardial perfusion measurements has been documented previously.^{5,24,25}

Secondary Study End Points

Signs of myocardial ischemia were assessed simultaneously with CFI measurement as quantitatively determined intracoronary ECG

ST-segment elevation (mV; Figure 2); the intracoronary ECG lead was obtained from the angioplasty guide wire via a cross-clamp to lead V_1 .^{3,5} Myocardial ischemia during the 1-minute coronary occlusions was also characterized by the presence or absence of angina pectoris.

Study Protocol

Before the diagnostic examination, 2 puffs of oral isosorbide dinitrate were given. After diagnostic coronary angiography and at the start of the invasive study procedure, all patients received 5000 U heparin intravenously. The left or right IMA was intubated via a second 5F right femoral artery introducer sheath using a 5F mammary artery guiding catheter. IMA angiography was performed (Figure 1). A 2.5-mm angioplasty balloon catheter (20 mm long) was placed distally at or slightly below the level of the heart. The coronary artery subsequently undergoing CFI measurements was chosen on the basis of the presence of a stenotic lesion requiring percutaneous coronary intervention or on the basis of ease of access in case of a nonstenotic vessel. A 6F coronary guiding catheter was used in all cases. Fractional flow reserve was obtained before CFI. Fractional flow reserve was determined with the pressure guide wire positioned distally in the nonoccluded vessel of interest with the use of an intracoronary bolus of ≈ 70 μ g adenosine for hyperemia induction: Fractional flow reserve equals distal coronary pressure divided by P_{ao} . Shortly before the first CFI measurement, the IMA angioplasty balloon was inflated at a pressure of 5 to 7 atm, and complete occlusion was established by angiography (Figure 1). During this vessel occlusion, simultaneous P_{occl} , P_{ao} , and CVP were obtained for the calculation of CFI (Figure 2). During the entire procedure, the intracoronary ECG obtained from the guide wire was recorded. At the end of the first 1-minute balloon occlusion, the IMA and the coronary artery angioplasty balloons were released in this sequence. Immediately after CFI measurement, the patient was asked about the occurrence of angina pectoris during the 1-minute coronary artery balloon occlusion. A few minutes after the combined occlusion of the IMA and coronary artery, the second coronary artery occlusion was performed with the angioplasty balloon at the identical location as in the first occlusion. The sequence of coronary occlusions remained unchanged throughout the study: first with and second without simultaneous IMA occlusion.

Statistical Analysis

Intraindividual comparison of CFI, intracoronary ECG ST-segment elevation, and heart rate obtained in the presence versus the absence of IMA occlusion was performed by a paired Student *t* test. A mixed linear model was used to assess the within-person correlation of repetitive measurements of continuous variables in >1 coronary artery. Because repetitive intraindividual measurements in different coronary arteries

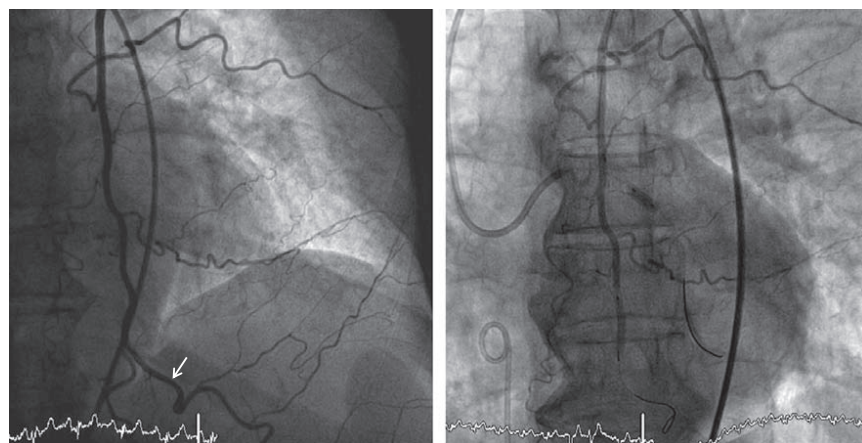


Figure 1. Left internal mammary artery (LIMA) angiographies in a patient before coronary angiography (**left**) and during simultaneous distal LIMA balloon occlusion with proximal occlusion of the left circumflex coronary artery (LCx; **right**). The LIMA occlusion is located at the bifurcation of the superior epigastric artery and the musculophrenic artery (arrow, **left**). During LIMA occlusion with radiographic contrast injection (**right**), the LCx is hazily imaged downstream of the balloon occlusion without delineation of a distinct vessel connecting the LIMA and LCx (pressure sensor wire positioned in a marginal branch).

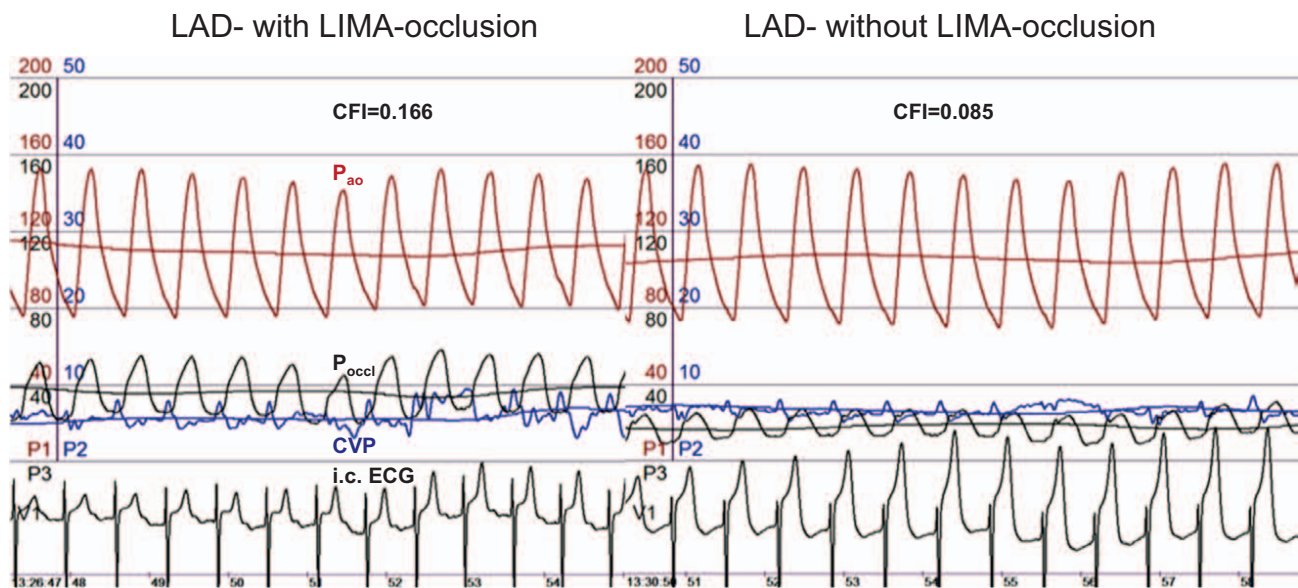


Figure 2. Coronary collateral flow index (CFI) measurement in a patient with balloon occlusion of the proximal left anterior descending artery (LAD) with (**left**) and without (**right**) simultaneous distal left internal mammary artery (LIMA) occlusion. **Left and Right,** Simultaneous recordings of phasic and mean aortic pressure (P_{ao} ; red line; scale, 200 mmHg), distal coronary occlusive pressure (P_{occ} ; black line; scale, 200 mmHg), and central venous pressure (CVP; blue line; scale, 50 mmHg). Additionally, an intracoronary (i.c.) ECG tracing is depicted at the **bottom**. The time is given at the bottom of the recording (≈ 4 minutes between the 2 LAD occlusions).

were not shown to be related to the study end points, between-group comparisons of continuous demographic, clinical, angiographic, and hemodynamic variables, CFI, and intracoronary ECG data were performed by factorial ANOVA followed by the Bonferroni post hoc test (values of $P < 0.0033$ indicating significance in the context of multiple testing). Study groups were established on the basis of the 6 different combinations of IMA with coronary artery occlusion. The χ^2 test or, when applicable, the Fisher exact test was used for comparison of categorical variables among the study groups. Continuous variables are given as mean and SD or SE or as median and interquartile range when applicable (nonnormal distribution of data).

Results

A total of 180 pairs of CFI measurements were performed among the 120 study patients, that is, 60 patients underwent 1 and 60 patients underwent 2 CFI measurements (Table 1). The prevalence of a functional IMA-to-coronary artery connection as defined by a larger CFI in the presence compared with the absence of IMA occlusion was 123 of 180 (68%). During IMA occlusion, CFI was 0.110 ± 0.074 ; in the absence of IMA occlusion, CFI was 0.096 ± 0.072 ($P < 0.0001$).

Patient Characteristics and Clinical Data

There were no statistically significant differences between the groups in terms of age, occurrence of cardiovascular risk factors, and intake of cardiovascular drugs (Table 1). The proportion of men differed significantly between the study groups (Table 1).

Hemodynamic and Coronary Angiographic Data

There was no difference between the groups in systemic blood pressure, left ventricular ejection fraction, and left ventricular end-diastolic pressure (Table 2). The number of coronary arteries with CAD, the total number of stenotic lesions, the percent diameter narrowing of the stenosis (vessel undergoing CFI measurement), and the fractional flow reserve obtained in the same vessel did not differ statistically between the groups (Table 2).

IMA Occlusion and Related Changes in Study End Points

IMA balloon occlusion time before coronary balloon occlusion was similar between the study groups (Table 3). Heart rate obtained during simultaneous IMA and coronary artery occlusion and during coronary occlusion without IMA occlusion did not differ either intraindividually ($P = 0.29$) or between the groups (Table 3).

Primary Study End Point

CFI obtained simultaneously with IMA occlusion was different between the study groups and was similar in the absence of IMA occlusion (Table 3). Figure 2 exemplifies an augmented CFI in the presence versus the absence of simultaneous IMA balloon occlusion. The individual changes in CFI in the presence versus the absence of IMA occlusion are shown in Figure 3.

The difference of CFI obtained in the presence of IMA occlusion minus CFI in the absence of IMA occlusion was highest and most consistently positive during left IMA with left anterior descending artery (LAD) occlusion and during right IMA with right coronary artery (RCA) occlusion (ipsilateral occlusions): 0.033 ± 0.044 and 0.025 ± 0.027 , respectively (Table 3 and Figure 4). This CFI difference was absent during right IMA with LAD occlusion and during left IMA with RCA occlusion (contralateral occlusions): -0.007 ± 0.034 and 0.001 ± 0.023 , respectively (Table 3 and Figure 4). The respective CFI differences during either IMA with left circumflex artery (LCx) occlusion were inconsistently positive (Table 3 and Figure 4).

In the 60 patients undergoing 2 coronary artery measurements, the mentioned CFI differences were statistically independent between the 2 coronary arteries: Δ CFI in the first vessel $= 0.01 \pm 0.1$ Δ CFI in the second vessel; $r^2 = 0.005$, $P = 0.61$ (Δ CFI is CFI with IMA occlusion minus CFI without IMA occlusion).

Table 1. Patient Characteristics and Clinical Data

	LAD–LIMA	LAD–RIMA	LCx–LIMA	LCx–RIMA	RCA–LIMA	RCA–RIMA	<i>P</i>
Patients, n	20	20	20	20	20	20	
CFI measurements, n	30	30	30	30	30	30	
Coronary artery–IMA connection	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Contralateral	Ipsilateral	
Age, y	69±8	61±8	67±8	61±12	65±12	63±11	0.09
Male sex, n (%)	8 (40)	17 (85)	10 (50)	14 (70)	15 (75)	14 (70)	0.0150
Body mass index, kg/m ²	28±8	29±5	27±6	27±6	27±6	27±5	0.90
Smoking, n (%)	3 (15)	7 (35)	7 (35)	8 (40)	4 (20)	5 (25)	0.23
Dyslipidemia, n (%)	11 (55)	12 (60)	12 (60)	12 (60)	11 (55)	13 (65)	0.81
Hypertension, n (%)	15 (75)	11 (55)	17 (85)	14 (70)	13 (65)	11 (55)	0.19
Family history of CAD, n (%)	7 (35)	8 (40)	7 (35)	8 (40)	8 (40)	7 (35)	0.99
Diabetes mellitus, n (%)	4 (20)	3 (15)	7 (35)	3 (15)	3 (15)	4 (20)	0.77
Acetylsalicylic acid, n (%)	13 (65)	12 (60)	11 (55)	12 (60)	12 (60)	11 (55)	0.71
Clopidogrel, n (%)	5 (25)	5 (25)	3 (15)	4 (20)	3 (15)	5 (25)	0.55
β-Blockers, n (%)	9 (45)	7 (35)	11 (55)	11 (55)	9 (45)	9 (45)	0.55
Nitrates, n (%)	0	0	1 (5)	0	1 (5)	0	0.45
ACE inhibitor/ARB, n (%)	11 (55)	9 (45)	12 (60)	10 (50)	12 (60)	10 (50)	0.74
Diuretics, n (%)	5 (25)	10 (50)	5 (25)	2 (10)	5 (25)	5 (25)	0.54
Statin, n (%)	11 (55)	11 (55)	12 (60)	14 (70)	12 (60)	13 (65)	0.68

Continuous values are given as mean±SD. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CFI, collateral flow index; IMA, internal mammary artery; LAD, left anterior descending artery; LCx, left circumflex coronary artery; LIMA, left internal mammary artery; RCA, right coronary artery; and RIMA, right internal mammary artery.

Secondary Study End Points

Figure 2 exemplifies reduced intracoronary ECG ST-segment elevation in the presence versus the absence of simultaneous IMA balloon occlusion. Intracoronary ECG ST-segment elevation normalized for R amplitude was diminished most during ipsilateral left IMA with LAD occlusion and during right IMA with RCA occlusion, whereas it remained unchanged or was worsened during contralateral IMA occlusion or during IMA with LCx occlusion, respectively (Table 3 and Figure 4). Angina pectoris tended to

be diminished during ipsilateral IMA with LAD and RCA occlusions (Table 3).

Discussion

The present clinical study demonstrated for the first time the prevalent in vivo function of natural IMA-to-coronary artery bypasses and their anti-ischemic effect. Functional natural IMA bypasses were consistently present during ipsilateral IMA with coronary artery occlusion (right IMA with RCA and left IMA with LAD); they were absent or inconsistently

Table 2. Hemodynamic and Coronary Angiographic Data

	LAD–LIMA	LAD–RIMA	LCx–LIMA	LCx–RIMA	RCA–LIMA	RCA–RIMA	<i>P</i>
CFI measurements, n	30	30	30	30	30	30	
Systolic blood pressure, mm Hg	132±30	125±20	126±24	124±21	123±23	119±21	0.25
Diastolic blood pressure, mm Hg	71±18	76±13	70±12	70±13	70±13	68±13	0.33
LV ejection fraction, %	64±8	64±8	64±11	59±9	66±7	62±6	0.08
LV end-diastolic pressure, mm Hg	12±6	11±7	12±6	14±17	11±7	15±15	0.61
Diseased vessels, n (%)							0.65
0	11 (37)	8 (27)	8 (27)	7 (23)	10 (33)	10 (33)	
1	7 (23)	7 (23)	6 (20)	4 (14)	4 (14)	4 (14)	
2	6 (20)	8 (27)	11 (37)	6 (20)	11 (37)	7 (23)	
3	6 (20)	7 (23)	5 (16)	13 (43)	5 (16)	9 (30)	
Total stenoses, n	1.5±2.0	1.2±1.6	1.4±1.4	1.8±2.1	1.3±1.5	1.6±2.0	0.76
Percent diameter stenosis	28±24	27±20	22±22	24±26	26±19	32±28	0.67
Fractional flow reserve	0.81±0.14	0.83±0.13	0.92±0.09	0.93±0.09	0.92±0.13	0.89±0.18	0.0112

Continuous values are given as mean±SD. CFI indicates collateral flow index; LAD, left anterior descending artery; LCx, left circumflex coronary artery; LIMA, left internal mammary artery; LV, left ventricular; RCA, right coronary artery; and RIMA, right internal mammary artery.

Table 3. IMA Occlusion and Related Changes in Coronary Collateral Function and Myocardial Ischemia

	LAD-LIMA	LAD-RIMA	LCx-LIMA	LCx-RIMA	RCA-LIMA	RCA-RIMA	P
CFI measurements, n	30	30	30	30	30	30	
IMA occlusion time before CFI, min	2.8±1.8	3.1±1.7	2.9±1.9	4.1±2.8	4.2±3.2	3.9±2.9	0.25
Heart rate with IMA occlusion, bpm	72±15	73±12	69±10	68±14	65±12	67±13	0.09
Heart rate without IMA occlusion, bpm	72±16	73±11	68±13	67±11	64±11	67±13	0.09
CFI with IMA occlusion	0.126±0.073*	0.070±0.043	0.122±0.070	0.125±0.086	0.102±0.074	0.116±0.079	0.0231
CFI without IMA occlusion	0.093±0.074	0.077±0.058	0.109±0.077	0.107±0.076	0.101±0.079	0.091±0.067	0.54
ΔCFI (with–without IMA occlusion)	0.033±0.04†	−0.007±0.03†	0.014±0.03	0.017±0.05	0.001±0.02	0.025±0.03	0.0002
ECG ST-segment elevation with IMA occlusion‡	0.82±1.76	0.54±0.65	0.41±0.36	0.26±0.19	1.06±2.10	1.18±2.21	0.13
ECG ST-segment elevation without IMA occlusion‡	1.36±2.91	0.65±0.78	0.41±0.30§	0.29±0.19§	0.60±0.99	1.78±2.51	0.0070
ΔECG ST-segment shift (with–without IMA occlusion)‡	−0.51±1.18	−0.11±0.58	−0.02±0.22	−0.03±0.19	0.48±1.64	−0.48±1.42	0.0092
No angina pectoris with vs without IMA occlusion, n (%)	3 (10)	0	1 (3)	2 (7)	0	3 (10)	0.08

Continuous values are given as mean±SD. CFI indicates collateral flow index; IMA, internal mammary artery; LAD, left anterior descending artery; LCx, left circumflex coronary artery; LIMA, left internal mammary artery; LV, left ventricular; RCA, right coronary artery; and RIMA, right internal mammary artery.

* $P<0.0029$ for LAD-LIMA vs LAD-RIMA. † $P\leq 0.0009$ for LAD-LIMA vs LAD-RIMA, LAD-LIMA vs RCA-LIMA, and LAD-RIMA vs RCA-RIMA.

‡ECG ST-segment elevation normalized for R-wave amplitude (mV/mV).

§ $P\leq 0.0030$ for LCx-LIMA vs RCA-RIMA and LCx-RIMA vs RCA-RIMA.

|| $P<0.0012$ for LAD-LIMA vs RCA-LIMA and RCA-LIMA vs RCA-RIMA.

present during contralateral IMA with coronary artery occlusion or during either IMA with LCx occlusion.

Extracardiac Coronary Collateral Supply

The branches of the IMAs are the pericardiophrenic arteries with their high takeoff, anterior intercostal arteries, perforating arteries, musculophrenic arteries, and superior epigastric arteries

(ie, the continuation of the IMAs), which finally anastomose with the external iliac arteries via the inferior epigastric arteries. In this article, the older term IMA is used instead of the newer term internal thoracic artery in the context of historical aspects relating to IMA surgery. The anatomy of extracardiac coronary arterial anastomoses taking their origin from the bronchial or the internal thoracic arteries was alluded to as early as

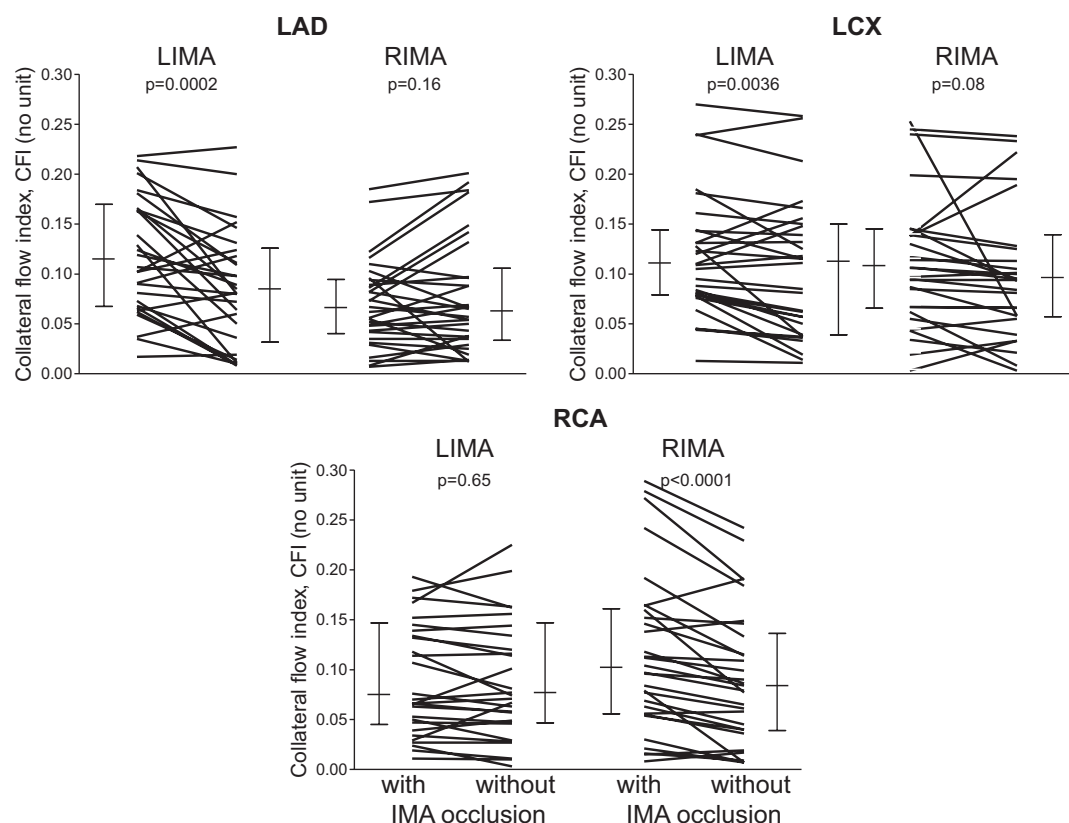


Figure 3. Individual changes in coronary collateral flow index (CFI) obtained in the 3 coronary arteries with and without simultaneous internal mammary artery (IMA) occlusion. The error bars indicate median values and interquartile ranges. LAD indicates left anterior descending artery; LCx, left circumflex coronary artery; LIMA, left IMA; RCA, right coronary artery; and RIMA, right IMA.

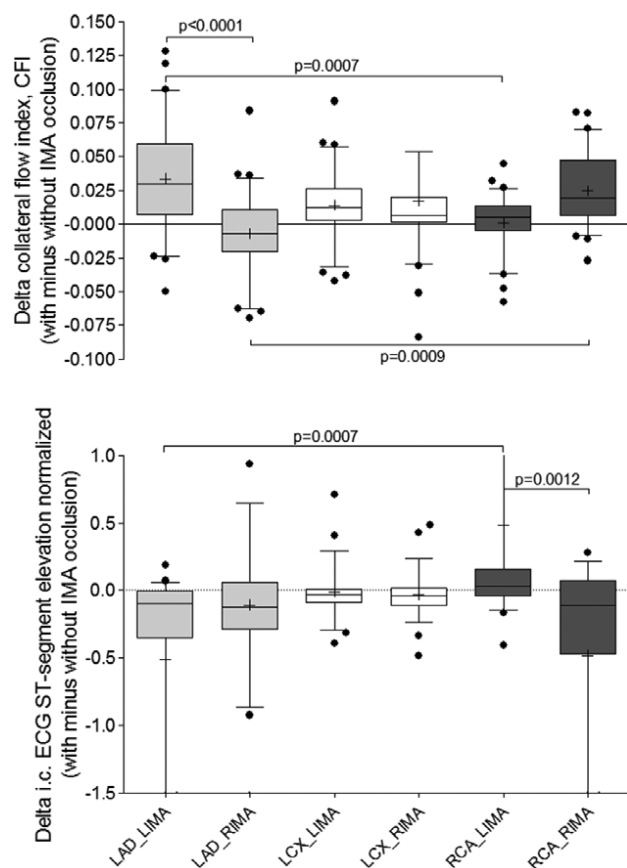


Figure 4. **Top,** Difference (Delta) between collateral flow index (CFI) obtained with internal mammary artery (IMA) occlusion and that obtained without IMA occlusion (vertical axis) plotted for the study groups (ie, according to the combination of IMA with simultaneous coronary artery occlusion). **Bottom,** Difference (Delta) between intracoronary ECG ST-segment elevation normalized for R amplitude obtained with IMA occlusion and that without IMA occlusion (vertical axis) plotted as in the **top**. The box plots indicate median values and interquartile ranges; the error signs indicate 10% and 90% confidence intervals; and the cross signs indicate mean values. LAD indicates left anterior descending artery; LCx, left circumflex coronary artery; LIMA, left IMA; RCA, right coronary artery; and RIMA, right IMA.

1803 by Albrecht von Haller (cited in Loukas et al²⁶). Hudson et al¹⁰ rediscovered them accidentally by observing the supply of ink injected into the coronary circulation to the pericardium and to extracardiac arterial regions. Hence, communication between the coronary circulation and pericardiacophrenic branches of the IMAs, but also the anterior mediastinal, phrenic, and intercostal arteries and the esophageal arterial branches of the aorta, was demonstrated.¹¹ The bronchial arteries supply the posterior part of the pericardium, and extracardiac anastomoses to the coronary arteries are preferentially found at sites of pericardial reflections such as entry into the pericardium of the caval veins.²⁷ The most common bronchial artery-to-coronary artery communication has been documented to the left circumflex coronary artery.²⁷ Structurally, this may explain why in our present study functional IMA bypasses to the LCx were present only inconsistently and why, in essence, they had no anti-ischemic effect.

Function of Natural IMA Bypasses

In the context of the first studies of bilateral IMA ligation (see below),^{12–16,28} canine experiments on the extracorporeal bypass

have shown that the procedure as carried out in the second intercostal space led to an average increase in total coronary flow of ≈ 6 to 10 mL/min.²⁹ It was thought that the hemodynamic effect of IMA ligation was transmitted by a local pressure rise of 12 to 15 mmHg in the subclavian artery with unchanged systemic pressure.³⁰ If the macroscopic arterial circulation is considered a system of connecting tubes, an instantaneous pressure equilibration would physically be expected rather than the mentioned pressure difference. Conversely, the length of the arterial system between different sections resisting the pressure transmission could serve as an explanation for the findings by Taber and Marchioro.³⁰

Compared with the cited experiments,^{29,30} the present study protocol did not, for ethical reasons, temporarily block the entire coronary circulation but instead blocked only part of it, that is, 1 of the 3 coronary arteries. Myocardial ischemia was induced twice with and without simultaneous IMA occlusion. The sequence of coronary occlusions with IMA occlusion first was held constant as a conservative measure favoring the null hypothesis of the study that coronary collateral function does not increase in the presence versus the absence of distal IMA balloon occlusion. Possible coronary collateral recruitment or ischemic preconditioning occurring during the second (but not the first) occlusion could be misinterpreted as augmented CFI or diminishing signs of ischemia in the context of IMA occlusion if it occurred during the second but not the first coronary occlusion. Despite this study design, CFI was higher in the presence versus the absence of IMA occlusion in 68% of the measurements, and overall, this difference amounted to 0.025 compared with the absence of IMA occlusion ($P<0.0001$). The fact that the anatomic vicinity of the occluded IMA and coronary artery rendered this finding more consistent enhances the verification of the hypothesis in the case of the LAD and RCA. The variability in response of either IMA occlusion during LCx occlusion increased rather than decreased, which may be seen in light of the variable supply of the LCx coronary territory by extracardiac sources other than the IMA (bronchial arteries).²⁷ The consistency of the CFI increase during IMA occlusion was slightly less in the case of LAD with left IMA occlusion (25 of 30 measurements) than in the case of RCA with right IMA occlusion (28 of 30 measurements). The most likely explanation for a worsening response in the context of ipsilateral IMA-to-LAD and IMA-to-RCA occlusions is strong collateral recruitment or ischemic preconditioning during the second coronary occlusion in nonfunctional IMA anastomoses. Theoretically, the possibility of the 20-mm-long angioplasty balloon obstructing the takeoff of the pericardiacophrenic branch directly supplying the coronary system is given as an alternative explanation for a diminished CFI during ipsilateral IMA occlusion. However, for this study, it is irrelevant because the IMA occlusion site was always distal at the fifth or sixth intercostal space, where the bifurcation of the superior epigastric and the musculophrenic artery is located (Figure 1A). The bifurcation of the IMA and the pericardiacophrenic artery is, on the other hand, its first or second one at the level of the first or second intercostal space.

Anti-Ischemic Effect of Natural IMA Bypasses

This topography of the IMA-pericardiacophrenic bifurcation provided the rationale for the IMA ligation site chosen in the trials

carried out in the late 1950s among ≈500 symptomatic CAD patients.^{15,17,18,28,31–33} IMA ligation as a treatment for angina pectoris was conceived by Fieschi in 1939, and in 1954, Battezzati et al¹² documented anew the existence of connections between both IMAs and the myocardium by methylene blue injection into the IMAs. Transthoracic surgical access to the IMAs was performed under local anesthesia by a small incision between the second and third rib. The primary end point of the clinical trials was angina pectoris and, inconsistently, ECG signs of myocardial ischemia. Battezzati and coworkers²⁸ reported the results of their uncontrolled trial among 304 CAD patients in 1959. Nearly all of the patients improved in terms of their symptoms, and this improvement was sustained during follow-up. In a further uncontrolled trial among 50 CAD patients, Kitchell et al³¹ reported similarly favorable results, with symptomatic relief in 68% of the patients. The following sham-controlled trials of bilateral IMA ligation in 35 CAD patients coined the phrase “surgery as placebo” in the context of their negative results.^{17,18,34} Although the introduction of a sham-control study design in the context of surgical trials was seminal,³⁵ the conclusion drawn from the negative results of the IMA ligation trials at hand is questionable in the context of the present investigation. Possibly in this context, the anti-ischemic concept of IMA ligation has been promoted again lately.^{22,36–38}

In the trial by Cobb et al,¹⁷ angina pectoris relief was found in 5 of 8 patients (63%) after IMA ligation and in 5 of 7 patients (71%) after IMA sham ligation. Dimond and coworkers¹⁸ reported 9 of 13 in the verum and 5 of 5 in the sham-operation group, respectively. In comparison, angina pectoris relief during a 1-minute ipsilateral IMA plus simultaneous coronary balloon occlusion in our study occurred in 6 of 60 measurements among 40 patients; it was absent during contralateral IMA occlusion ($P=0.08$). From this perspective, the abrupt stop of bilateral transthoracic IMA ligation was likely caused by the advent of IMA bypass grafting rather than by the slim evidence against IMA ligation claimed by the controlled trials. The soft study end point of angina pectoris requires patient numbers that, for meaningful results, are 1 order of magnitude higher than those recruited for the sham-controlled IMA ligation trials. This is even more so in case of an inconsistently applied ischemic stimulus such as daily activities versus the systematically used 1-minute coronary occlusion. In this context, the present study predefined intracoronary ECG ST-segment elevation during coronary occlusion, not angina pectoris, as the first end point for ischemia, the former of which was consistently reduced during ipsilateral IMA with RCA or LAD occlusion. Another drawback of the historical IMA ligation studies was that their patients did not undergo coronary angiography, and it is unknown how many in the verum group had, by chance, their culprit lesion in the LCx, where the effect of IMA ligation from either side is variable and not anti-ischemic. Finally, the systematic IMA ligation at the second intercostal space may have resulted in a variable site of IMA occlusion proximal or distal to the pericardiophrenic artery, that is, the source of extracardiac supply to the coronary circulation. Occlusion proximal to the bifurcation of the pericardiophrenic artery likely resulted in a much reduced supply to the pericardium compared with distal occlusion.

Study Limitations

The present study performed collateral function measurements of the IMAs themselves in only a small minority of the cases,

which does not allow reliable estimation of their CFI for a distinction between the effect of proximal and distal IMA occlusion. Anatomically, there is communication between the IMAs and the iliac external arteries via the superior and inferior epigastric arteries. On the basis of the rare functional IMA CFI measurements of the present study, collateral supply from the caudal side amounted to approximately two thirds during proximal IMA occlusion compared with patency. The absence of systematic proximal IMA occlusion implies a further study limitation, that is, the missing information on the effect of proximal IMA occlusion together with occlusion of the pericardiophrenic branch. Because the latter has been described as the extracardiac source of coronary arterial supply, the effects found in the present study would have been absent during proximal IMA occlusion at the site of the pericardiophrenic artery bifurcation. Finally, IMA angiography during distal occlusion was systematically performed, but image quality at the end of the 1-minute occlusion was too inconsistent to allow proper analysis of contrast medium supply to the coronary circulation. In fact, this could be seen in only 2 to 3 patients in our study (see Figure 1).

Study Implications

From the present study findings, an anti-ischemic therapeutic approach alternative to IMA bypass grafting (ie, distal IMA occlusion by invasive techniques) can be considered. In a first step, catheter-based IMA occlusion ought to be investigated conceptually in the setting of the less frequently grafted right IMA among patients with ischemia in the RCA territory.

Conclusion

There is a functional, ischemia-reducing extracardiac coronary artery supply via ipsilateral but not via contralateral natural IMA bypasses.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Until now, the prevalence, functional relevance, and effect on myocardial ischemia of extracardiac coronary collateral supply via natural internal mammary artery (IMA) bypasses have been unknown. The present study in patients without and with coronary artery disease tested the hypotheses that coronary collateral function increases in the presence versus the absence of distal IMA balloon occlusion and that the former is reflected by reduced myocardial ischemia. The study among 120 patients with chronic stable coronary artery disease undergoing coronary angiography found that there is a functional, ischemia-reducing extracardiac coronary artery supply via ipsilateral (ie, during left IMA with left anterior descending artery occlusion and during right IMA with right coronary artery occlusion) but not via contralateral natural IMA bypasses. On the basis of the findings presented here, an anti-ischemic therapeutic approach alternative to IMA bypass grafting, that is, distal IMA occlusion by invasive techniques, can be considered. In a first step, catheter-based IMA occlusion ought to be conceptually investigated in the setting of the less frequently grafted right IMA among patients with ischemia in the right coronary artery territory.

3.2 Project II

Effect of Permanent Right Internal Mammary Artery Closure on Coronary Collateral Function and Myocardial Ischemia

The second project aimed at determining the effect of permanent right internal mammary closure on coronary collateral function and myocardial ischemia in humans.

My contributions were the conception and design of the project, acquiring, analyzing and interpreting the data, assisting in statistical analysis and making critical revision of the manuscript for important intellectual content.

The paper has been published in *Circulation: Cardiovascular Interventions* in June 2017, journal ranking was #13 according to impact factor and #8 according to SCImago Journal Rank (SJR)[89] in 2015 in Cardiology and Cardiovascular Medicine.

Effect of Permanent Right Internal Mammary Artery Closure on Coronary Collateral Function and Myocardial Ischemia

Michael Stoller, MD; Christian Seiler, MD

Background—The objective of this study is to test the effect of permanent right internal mammary artery device closure on coronary collateral function and myocardial ischemia.

Methods and Results—This was a prospective, open-label clinical trial in 50 patients with coronary artery disease. The primary study end point was coronary collateral flow index as obtained during a 1-minute proximal right coronary artery (RCA) and left coronary artery balloon occlusion at baseline before and at follow-up examination 6 weeks after distal right internal mammary artery device closure. Collateral flow index is the ratio between simultaneously recorded mean coronary occlusive pressure divided by mean aortic pressure, both subtracted by central venous pressure. Secondary study end points were fractional flow reserve during vessel patency, the quantitative intracoronary ECG ST-segment elevation, and angina pectoris during the same 1-minute coronary occlusion. Collateral flow index in the untreated RCA and left coronary artery changed from 0.071 ± 0.082 at baseline to 0.132 ± 0.117 ($P < 0.0001$) at follow-up examination and from 0.106 ± 0.092 to 0.081 ± 0.079 ($P = 0.29$), respectively. RCA fractional flow reserve increased significantly ($P = 0.0029$) from baseline to follow-up examination, despite deferral of coronary intervention in all patients. There was a decrease in intracoronary ECG ST-elevation during RCA occlusion from baseline to follow-up examination ($P = 0.0015$); it did not change in the left coronary artery. Angina pectoris during RCA occlusion tended to occur in fewer patients at follow-up versus baseline examination ($P = 0.06$).

Conclusions—Permanent right internal mammary artery device closure seems to augment extracardiac ipsilateral coronary supply to the effect of reducing ischemia in the dependent myocardial region.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02475408.

(*Circ Cardiovasc Interv*. 2017;10:e004990. DOI: 10.1161/CIRCINTERVENTIONS.116.004990.)

Key Words: arteriogenesis ■ collateral circulation ■ coronary circulation ■ internal mammary artery ■ myocardial ischemia

The prevalence of patients with stable coronary artery disease (CAD) undergoing indicated but incomplete revascularization is close to 30%, and all-cause mortality among these patients has been described elevated in comparison to those with complete revascularization (3-year cumulative mortality rate of 14.8% versus 6.6%).¹ Patients with incomplete revascularization and refractory angina pectoris require novel therapeutic strategies aimed at improving survival by reducing myocardial ischemia because in stable CAD, outcome after medical therapy irrespective of percutaneous coronary intervention (PCI) is dependent on the amount of myocardial ischemia.² In the event of coronary occlusion, ischemia is influenced by its duration, the size of the ischemic territory, the lack of collateral supply, the absence of ischemic preconditioning prior to occlusion, and myocardial oxygen consumption at the time of occlusion.³ The clinical benefit on survival of a functional

intercoronary collateral circulation in chronic stable CAD has been documented.^{4,5} Additionally, extracardiac coronary collateral supply via the internal mammary artery (IMA) has been described.^{6–8} Seven case reports have documented the existence of naturally occurring angiographic anastomoses between one of the IMAs and the human coronary circulation.^{9–15} Blair et al measured increased coronary artery blood flow after experimental IMA ligation. More recently, a study in 8 dogs undergoing coronary artery constriction and IMA ligation has failed to reveal myocardial microsphere perfusion via IMA in the single animal, which survived the study protocol.¹⁷ In patients with CAD, our group has provided evidence for a functional, ischemia-reducing extracardiac coronary artery collateral supply during temporary ipsilateral IMA balloon occlusion.¹⁸

See Editorial by Kern and Seto

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WHAT IS KNOWN

- A recent investigation in patients with stable coronary artery disease has shown that temporary balloon occlusion of the internal mammary artery induces a functional, ischemia-reducing extracardiac coronary artery supply via ipsilateral natural internal mammary artery bypasses.

WHAT THE STUDY ADDS

- The new finding of the present study is that over the course of 6 weeks, permanent right internal mammary artery occlusion by a vascular closure device augments extracardiac right coronary artery but not left coronary artery supply and reduces myocardial ischemia during a 1-minute ostial right coronary artery balloon occlusion.
- Permanent internal mammary artery device closure deserves further evaluation as a potential treatment option for alleviation of myocardial ischemia in patients with chronic coronary artery disease not amenable to conventional revascularization or refractory to medical therapy.

Thus, the present conceptual study tested the hypotheses that after 6 weeks of follow-up, permanent right IMA (RIMA) device closure results in augmented collateral function of the right coronary artery (RCA), but not the left coronary artery (LCA), and that this is reflected by respective changes in myocardial ischemia.

Methods

Study Design and Patients

This was a prospective, open-label, longitudinal interventional clinical trial in 50 patients undergoing diagnostic coronary angiography in the context of chest pain. The primary study end point was quantitative coronary collateral function (collateral flow index, CFI; see below for calculation) as obtained during a 1-minute proximal coronary artery balloon occlusion at baseline before and at follow-up examination 6 weeks after RIMA device occlusion (Figure 1). Secondary study end points were fractional flow reserve during vessel patency (FFR), the quantitatively determined intracoronary (IC) ECG ST-segment elevation, and angina pectoris during the same 1-minute coronary occlusion. Study end points were obtained in the RCA and LCA. Eligibility criteria for study inclusion were age >18 years, angina pectoris under conventional medical therapy, written informed consent to participate in the study, and 1- to 3-vessel chronic stable CAD. Exclusion criteria were acute coronary syndrome, previous myocardial infarction in the vascular region undergoing CFI measurement, and severe hepatic or renal failure (creatinine clearance <15 mL/min per 1.73 m²).

The study was approved by the ethics committee of the Kanton of Bern, Switzerland, and all patients gave written informed consent to participate (in accordance with the author guidelines of this journal).

Cardiac Catheterization and Coronary Angiography

Patients underwent left heart catheterization and coronary angiography for diagnostic purposes from the right femoral artery approach via a 6F introducer sheath. Biplane left ventriculography was performed followed by coronary angiography. Coronary artery stenoses were

assessed quantitatively as percent diameter reduction using the guiding catheter for calibration. Aortic pressure (P_{ao}) was acquired via a 6F guiding catheter. Central venous pressure (CVP) was measured by a 5F pigtail catheter as right atrial pressure via the right femoral vein.

Study End Points

Primary Study End Point

Coronary occlusive collateral flow relative to normal antegrade flow through the nonoccluded coronary artery (CFI) was determined using coronary pressure measurements. A 0.014-inch pressure monitoring angioplasty guidewire (Pressure Wire; St Jude Medical, Eschborn, Germany) was set at zero, calibrated, advanced through the guiding catheter, and positioned in the distal part of the vessel of interest (identical position at baseline and follow-up examination). CFI was determined by simultaneous measurement of mean aortic pressure (P_{ao} , mmHg), the mean distal coronary artery pressure during balloon occlusion (P_{occl} , mmHg), and the mean CVP (mmHg; Figure 2) as measured during the last 30 seconds of the 1-minute coronary balloon occlusions. CFI was calculated as $(P_{occl} - CVP)$ divided by $(P_{ao} - CVP)$.¹⁹ The accuracy of pressure-derived CFI measurements in comparison to ECG signs of myocardial ischemia during occlusion and to absolute myocardial perfusion measurements has been documented previously.^{5,19–21}

Secondary Study End Points

Coronary pressure-derived FFR measurements were obtained. Signs of myocardial ischemia were assessed simultaneously to CFI measurement as quantitatively determined IC ECG ST-segment elevation in millivolt (Figure 2); the IC ECG lead was obtained from the angioplasty guidewire via a cross-clamp to a precordial lead.²² Myocardial ischemia during the 1-minute coronary occlusions was also characterized by the presence or absence of angina pectoris.

Study Protocol

Before the diagnostic examination, 2 puffs of oral isosorbidedinitrate were given. After diagnostic coronary angiography and at the start of the invasive baseline and follow-up study procedure, all patients received 5000 U of heparin intravenously. End point measurements were first obtained in the LCA, followed by the RCA. FFR was performed prior to CFI and in the same vessels as those undergoing CFI measurement. FFR was determined with the pressure guidewire positioned distally in the nonoccluded main vessel of interest using intravenous adenosine at 140 µg/min per kg for hyperemia induction: $FFR = \text{distal coronary pressure} / P_{ao}$. The LCA (left anterior descending artery, LAD, and left circumflex coronary artery) undergoing CFI measurements was chosen on the basis of the presence of a stenotic lesion requiring PCI or on the basis of ease of access in case of a nonstenotic vessel. For CFI, an adequately sized angioplasty balloon catheter was positioned in the ostial part of the vessel while the pressure guidewire remained distally. Before imminent coronary balloon occlusion, the patient was asked not to talk and to breathe normally for the following 1.5 minutes (prevention of CVP variability). Coronary balloon inflation occurred at a pressure of 1 to 2 atmospheres. Complete coronary occlusion was ascertained by angiography. During the 1-minute occlusion, simultaneous P_{occl} , P_{ao} , and CVP were recorded for the calculation of CFI (Figure 2). During the entire procedure, the IC ECG obtained from the guidewire was recorded. Immediately after CFI measurement, the patient was asked about the occurrence of angina pectoris during coronary artery balloon occlusion. At an $FFR > 0.75$, PCI of the LCA was deferred to the end of the invasive follow-up examination (ie, after all end point measurements), which took place at 6 weeks after the baseline examination; at an $FFR \leq 0.75$, PCI of the LCA occurred at baseline before end point measurements in the RCA. End point measurements in the RCA were repeated as just described.

At the end of the baseline examination, permanent RIMA device occlusion was performed using a 4F IMA catheter and a Radiofocus 0.032-inch, 260-cm stiff guidewire (Terumo, Eschborn, Germany), the latter of which was placed with its tip below the diaphragm. The IMA catheter was then exchanged for a 4F multipurpose catheter, which was engaged in the IMA until its tip reached the level of the right atrium

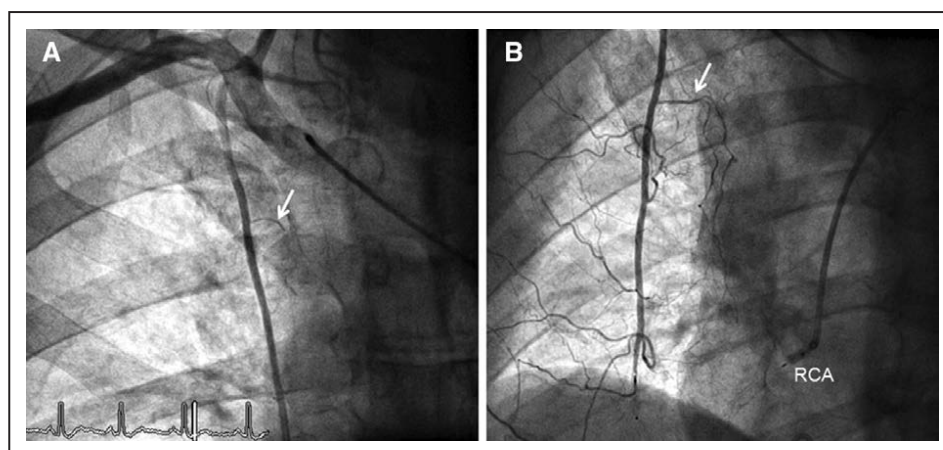


Figure 1. **A**, Anteroposterior angiogram of the truncus brachiocephalicus (site of the catheter tip) depicting the right internal mammary artery (RIMA) with its pericardiophrenic branch (arrow) taken at the baseline examination. **B**, RIMA angiography of the same patient as in **A** taken during follow-up examination. Simultaneous occlusion of the distal RIMA (by vascular occlusion device) and the ostial right coronary artery (RCA, by angioplasty balloon). The pericardiophrenic branch (arrow) and the other RIMA branches are larger than those at baseline (**A**).

(anteroposterior projection). Subsequently, an Amplatzer vascular plug 4 (St Jude Medical, Eschborn, Germany) was inserted via the multipurpose catheter into the RIMA at the level of the right atrium (Figure 1). Invasive follow-up examinations at 6 weeks after RIMA device occlusion consisted of identical measurements as described earlier.

Statistical Analysis

Sample size calculation was based on values for the primary end point CFI found in the previous work by Stoller et al,¹⁸ which had means±standard deviations of 0.116 ± 0.079 and 0.091 ± 0.067 with and without RIMA balloon occlusion, respectively, measured cross-sectionally. Using a 1-sided paired Student's *t* test for intraindividual changes and a correlation of 0.65 between the matched data pairs (baseline and 6-week follow-up RCA CFI), an alpha level of 0.05, and a power of 0.80, the calculated sample size was 40 using the GPower program. For the purpose of data presentation, 2 study groups were established based on the absence or presence of percent diameter RCA stenosis \leq or $>50\%$ as determined quantitatively. Intraindividual comparison of CFI, FFR, IC ECG ST-segment elevation, and heart rate obtained at baseline versus follow-up examination was performed by a paired Student's *t* test. Between-group comparison of continuous demographic, clinical, angiographic, hemodynamic variables, CFI, FFR, and IC ECG data was performed by unpaired Student's *t* test.

A χ^2 test was used for comparison of categorical variables among the study groups. Statistical significance was defined at a *P* level <0.05 . Continuous variables are given as mean and standard deviation.

Results

Thirty-seven patients belonged to the group with an RCA lesion $\leq 50\%$ in diameter, and 13 patients were in the group with at least 1 stenosis $>50\%$ (Table 1). PCI of the RCA was postponed to after follow-up end point measurements or not performed ($n=40$) in all 50 patients; in case of the LCA, PCI was deferred in 33 patients, and it was performed at baseline in 11 patients. In 6 patients, no LCA end point measurement at baseline and follow-up was performed, that is, it occurred only in the RCA.

Patient Characteristics and Clinical Data at Baseline

There were no statistically significant differences between the groups regarding age, sex, body mass index, Canadian Cardiovascular Society class of angina pectoris, cardiovascular risk factor prevalence, and cardiovascular medication (Table 1).

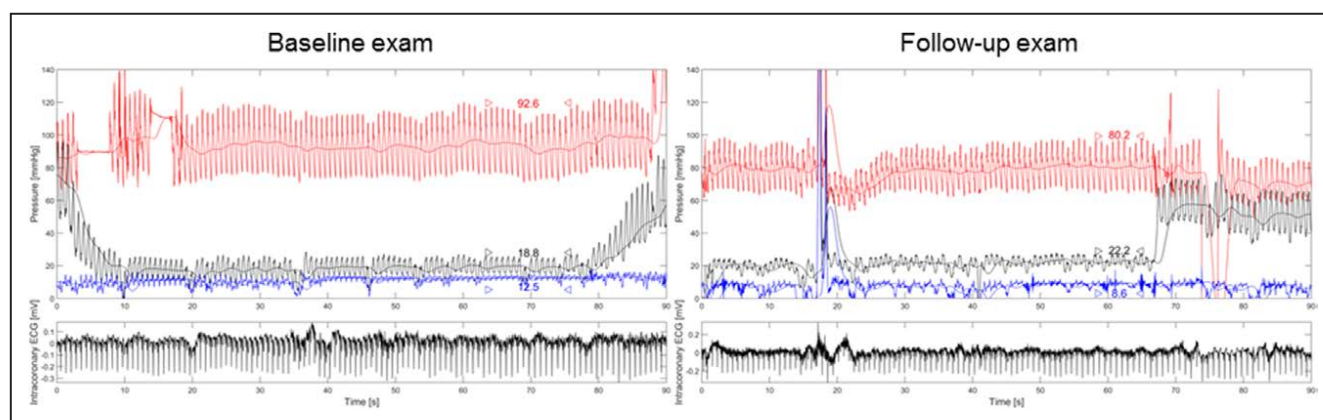


Figure 2. **Left**, Simultaneous recording of phasic and mean aortic pressure (P_{ao} , red curve), ostial right coronary artery (RCA) occlusive pressure (P_{occl} , black curve), central venous pressure (CVP, blue curve), and intracoronary ECG (bottom, black curve) as obtained during baseline examination. Coronary balloon occlusion starts at ≈ 2 seconds on the time scale (horizontal axis) and lasts until 79 seconds (up-slope of P_{occl}). P_{ao} , P_{occl} , and CVP are taken as temporal mean values between the arrowheads: collateral flow index, $CFI = (P_{occl} - CVP) / (P_{ao} - CVP) = (18.8 - 12.5) / (92.6 - 12.5) = 0.079$. **Right**, Simultaneous recording of phasic and mean P_{ao} , ostial RCA P_{occl} , CVP, and intracoronary ECG during follow-up examination in the same patient as in the **left** panel. $CFI = 0.190$.

Table 1. Patient Characteristics and Clinical Data at Baseline

	RCA % Diameter Reduction $\leq 50\%$	RCA % Diameter Reduction $> 50\%$	P Value
Number of patients	37	13	
Age, y	67 \pm 10	60 \pm 13	0.06
Male sex, %	31 (84)	13 (100)	0.17
Body mass index, kg/m ²	28 \pm 5	27 \pm 2	0.40
CCS class of angina at baseline 0/i/ii/iii	0/12/18/7	0/5/4/4	0.44
Current smoking, %	9 (24)	5 (38)	0.47
Dyslipidemia, %	35 (95)	12 (92)	0.98
Hypertension, %	28 (76)	10 (77)	0.95
Family history for CAD, %	15 (41)	3 (23)	0.49
Diabetes mellitus, %	12 (32)	1 (8)	0.14
Acetylsalicylic acid (ASA; %)	34 (92)	12 (92)	0.79
Platelet inhibitors other than ASA, %	14 (38)	6 (46)	0.34
Beta-blockers, %	23 (62)	6 (46)	0.52
Calcium antagonists, %	5 (14)	0	0.37
ACE inhibitor/ARB, %	28 (76)	10 (77)	0.82
Diuretics, %	7 (19)	2 (15)	0.80
Nitrates, %	3 (8)	0	0.56
Statins, %	33 (89)	12 (92)	0.60

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; and RCA, right coronary artery.

Hemodynamic and Coronary Structural and Functional Data at Baseline

There were no statistical differences between the groups in heart rate, left ventricular ejection fraction and end-diastolic pressure, and mean arterial venous pressure and CVP (Table 2). The number of coronary arteries with stenotic lesions $> 50\%$ was similar between the groups. Study end points were determined in all patients in the RCA and with similar frequency among the groups in the LAD or left circumflex coronary artery (in 44 LCA vessels at baseline). RCA percent diameter stenosis and FFR differed according to the group definition (Table 2). FFR of the LCA was significantly higher in the group with no or irrelevant RCA stenosis than in the group with significant RCA stenosis.

Changes of Coronary Function and Myocardial Ischemia During Follow-Up

Primary Study End Point

Overall, CFI in the RCA changed from 0.071 ± 0.082 at baseline to 0.132 ± 0.117 ($P < 0.0001$) at follow-up examination (Figure 3 and Table 2). CFI in the untreated LCA changed from 0.106 ± 0.092 to 0.081 ± 0.079 ($P = 0.29$). Absolute CFI change in the RCA over the 6-week course of follow-up was $+0.067 \pm 0.094$, and it was -0.012 ± 0.112 in the LCA ($P < 0.0001$; Figure 3). There was a trend to higher CFI increase in the group of patients with relevant RCA stenosis (Table 2).

Table 2. Hemodynamic Data at Baseline and Coronary Structural and Functional Data

	RCA % Diameter Reduction $\leq 50\%$	RCA % Diameter Reduction $> 50\%$	P Value
Number of patients	37	13	
Heart rate, bpm	72 \pm 12	73 \pm 15	0.92
Left ventricular ejection fraction, %	60 \pm 11	59 \pm 9	0.56
Left ventricular end-diastolic pressure, mm Hg	14 \pm 4	14 \pm 7	0.80
Mean arterial pressure, mm Hg	95 \pm 17	91 \pm 17	0.41
Mean central venous pressure, mm Hg	9 \pm 4	10 \pm 3	0.40
Number of coronary arteries diseased	2.3 \pm 0.7	2.4 \pm 0.7	0.58
Coronary artery for collateral flow index (CFI)			0.45
Right coronary artery (RCA), %	All	All	
Left anterior descending artery (LAD), %	13 (35)	6 (46)	
Left circumflex artery (LCX), %	21 (57)	4 (31)	
Right coronary artery PCI, %; all deferred	1 (3)	9 (69)	0.0001
Left coronary artery (LCA) PCI, %	34 (92)	10 (77)	0.61
Percent diameter stenosis RCA at baseline	28 \pm 18	65 \pm 23	< 0.0001
Percent diameter stenosis LCA at baseline	44 \pm 18	53 \pm 26	0.19
Fractional flow reserve RCA at baseline	0.89 \pm 0.12	0.75 \pm 0.26	0.0304
Fractional flow reserve LCA at baseline	0.84 \pm 0.10	0.66 \pm 0.24	0.0047
Collateral flow index RCA at baseline	0.063 \pm 0.073	0.090 \pm 0.111	0.36
Collateral flow index RCA at follow-up	0.116 \pm 0.082	0.146 \pm 0.143	0.39
CFI difference (follow-up minus baseline)	+0.053 \pm 0.065	+0.094 \pm 0.128	0.14
IC ECG ST-segment shift RCA at baseline, mV	+0.56 \pm 0.52	+0.42 \pm 0.59	0.53
CCS class of angina at follow-up 0/i/ii/iii	16/8/9/4	6/5/1/1	0.37

CCS indicates Canadian Cardiovascular Society; IC, intracoronary; and PCI, percutaneous coronary intervention.

Secondary Study End Points

FFR in the RCA increased significantly from baseline to follow-up examination (Figure 4), and it remained unchanged in the LCA (PCI deferred until after FFR measurement in all vessels). There was a decrease in IC ECG ST-elevation during

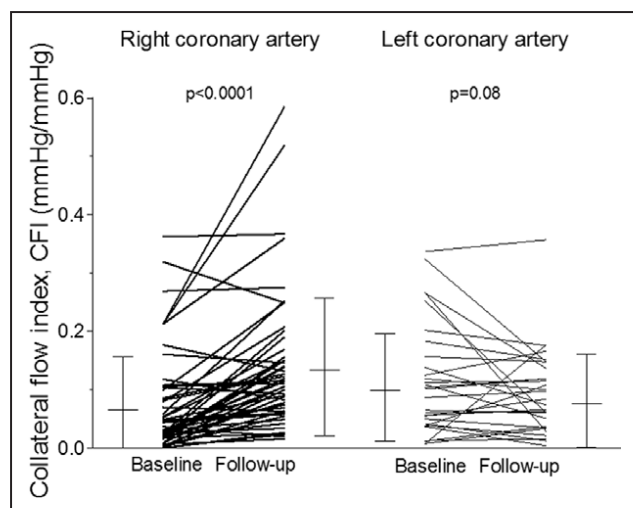


Figure 3. Individual values of collateral flow index (CFI, vertical axis) as obtained at baseline and follow-up examination in the right and left coronary artery. Error bars indicate mean values and standard deviation.

RCA occlusion from baseline to follow-up examination (Figure 4); IC ECG ST-elevation did not change significantly in the LCA. There was a trend to fewer events of angina pectoris during RCA occlusion at follow-up versus baseline examination and in comparison to LCA occlusion irrespective of the examination (Figure 5).

Canadian Cardiovascular Society class of angina pectoris class 0 at follow-up was observed more frequently than at baseline examination (Tables 1 and 2).

Procedural Feasibility of RIMA Closure

RIMA device closure was successful in all patients. In 12 patients, the right femoral artery access had to be switched to right radial artery or right brachial artery (n=2) access to achieve procedural success. Except for 2 cases of proximal RIMA dissection, no procedure-related complications

occurred. The dissections were left untreated. During the 6 weeks of follow-up, all patients remained asymptomatic with regard to the RIMA device closure. Angiographic control of the RIMA at follow-up revealed incomplete occlusion at the site of the device in 11 of 50 cases.

Discussion

The present conceptual clinical trial found that permanent RIMA device closure results in augmented right (but not left) coronary collateral function (CFI), which was reflected by improved coronary hemodynamics as obtained during vessel patency (FFR) and by reduced signs of myocardial ischemia during vessel occlusion.

Treatment Options for Refractory Angina Pectoris

Refractory angina pectoris is defined as a chronic condition (>3 months) characterized by the presence of angina caused by coronary insufficiency in the presence of CAD, which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery.²³ There are numerous treatment options aiming at alleviating myocardial ischemia using angiogenic therapeutic approaches (by the so-called myocardial laser revascularization,²⁴ external shock wave therapy,²⁵ and myocardial stem cell application²⁶), diastolic coronary pressure augmentation by external counterpulsation,²⁷ coronary arteriogenesis with induction of large collateral artery remodeling,²⁸ coronary sinus venous backpressure augmentation,^{29,30} and ischemic preconditioning.^{31,32} The latter represents the default therapy applied by any primary or secondary prevention program because physical exercise with myocardial ischemia is its cornerstone. The only potentially useful treatment option exerting a permanent and not just temporary effect is coronary sinus pressure augmentation using a venous caliber reducer stent.³³ All the other modalities require repetitive applications for a lasting effect, the fact of which substantially reduces the tolerability of a procedure, especially if it

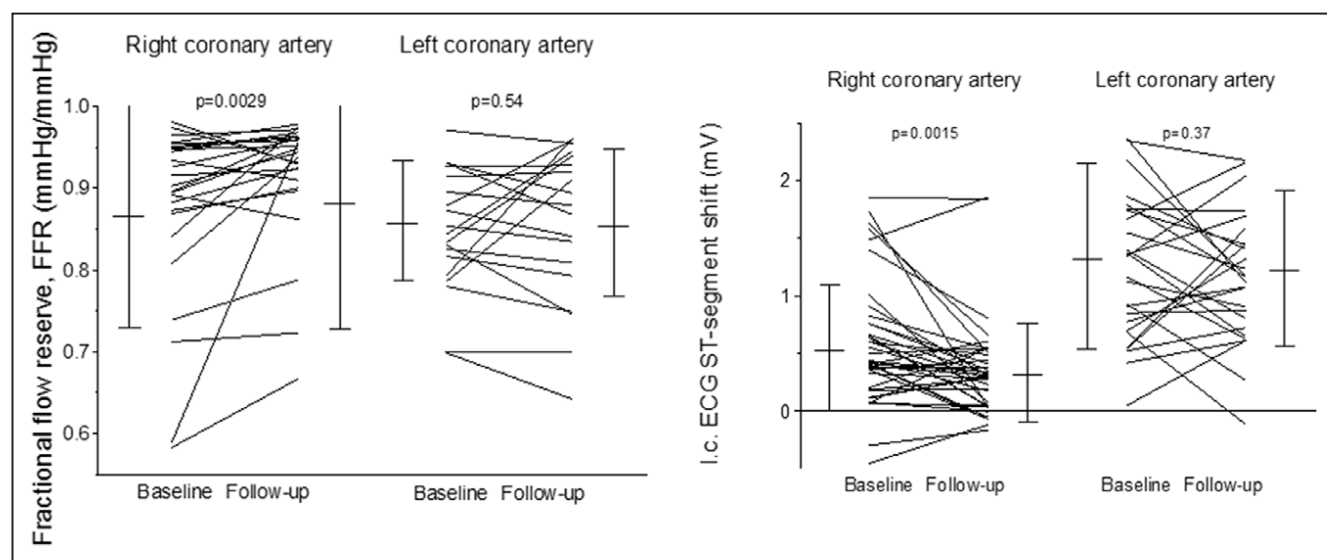


Figure 4. Left, Individual values of fractional flow reserve (FFR, vertical axis) as obtained at baseline and follow-up examination in the right and left coronary artery. Error bars indicate mean values and standard deviation. Right, Individual values of intracoronary ECG ST-segment shift (i.c. ECG ST-segment shift, vertical axis; ST-elevation as positive values) as obtained at baseline and follow-up examination in the right and left coronary artery. Error bars indicate mean values and standard deviation.

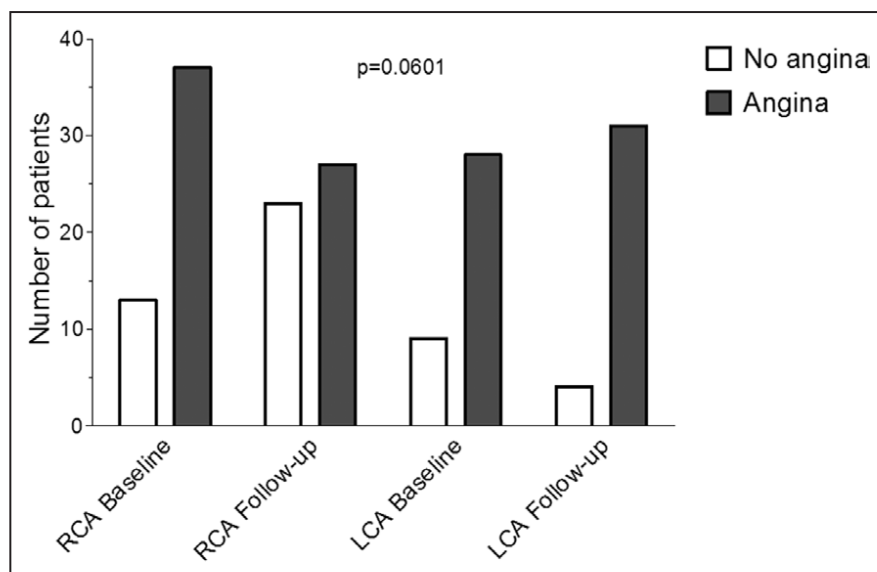


Figure 5. Number of patients with and without angina pectoris (vertical axis) during the 1-minute proximal right coronary artery (RCA) and left coronary artery (LCA) balloon occlusions at baseline and follow-up examination, which were performed for simultaneous pressure and intracoronary ECG measurements (see also Figure 2).

is as strenuous and time-consuming as, for example, external counterpulsation with its daily 1-hour sessions.

In comparison, the anatomic connections between the IMAs and the coronary circulation represent the basis for a sustainably improved extracardiac myocardial supply source.⁸ Essentially, this applies also to the extracardiac source of collateral connections between the bronchial artery and the RCA, respectively, the left circumflex coronary artery.³⁴ However, these circulatory anastomoses are even less explored than the IMA coronary artery network.

Extracardiac Coronary Artery Supply via the IMAs

Anatomically, the IMAs on each side and the coronary circulation are connected via the second IMA branch, that is, the pericardiophrenic or pericardiocophrenic artery, which takes off proximally at the second intercostal space and supplies the pericardium.⁸ During IMA angiography, the pericardiophrenic branch is recognizable as the only IMA branch moving with the heart beat. At the follow-up examination of our study, enlargement of this IMA branch could be observed often (see Figure 1). The pericardiophrenic artery with its pericardial branches finds access to atrial branches of the epicardial coronary circulation via the sites of pericardial reflections located at the entry into the pericardium of the caval veins.³⁵ This well-documented anatomic knowledge^{6-8,35,36} led to the first surgical attempt of myocardial revascularization. More than 20 years before the first clinical coronary artery bypass grafting in 1960,³⁷ the ligation of the IMAs aiming at redirecting blood flow to the pericardiophrenic branch was introduced as a treatment concept for angina pectoris by Fieschi.³⁸ In the course of this procedure, transthoracic surgical access to the IMAs was gained under local anesthesia by a small incision between the second and third rib, and they were ligated via this entry site. The primary end point of the first clinical IMA ligation trials was angina pectoris and, inconsistently, ECG signs of myocardial ischemia. Battezzati et al³⁹ reported the results of their uncontrolled trial in 304 CAD patients, with only half of them having angina pectoris: the symptoms of nearly all of them had improved sustainably. In a further uncontrolled trial among 50 CAD patients (2/3 with angina pectoris), Kitchell

et al⁴⁰ reported similarly favorable results with symptomatic relief in 68% of the patients.

Surgical bilateral IMA ligation has not gained historical stature because of its success, but because of its failure. The latter was—apparently—exposed by the then introduced new research design tool of a sham control group. The small, but sham-controlled negative trials by Cobb et al⁴¹ and by Dimond et al⁴² (totaling 35 patients) coined the term surgery as placebo.^{43,44} The fraction of trial participants (based on single digit numbers) experiencing relief of angina pectoris during long-term follow-up was similar between the really and sham-operated group.^{41,42} To infer IMA ligation inefficacious on the basis of those trials was unwarranted, but desirable for the inauguration of an essential scientific element into clinical research; this must be the current conclusion because of their low power in connection with a soft primary clinical end point (chest pain).

Furthermore, a recent clinical investigation in 120 CAD patients undergoing temporary distal IMA and simultaneous ostial coronary artery balloon occlusion has found an ischemia-reducing, enhanced extracardiac coronary artery supply via ipsilateral (but not contralateral) natural IMA bypasses.¹⁸ Specifically, the CFI difference as obtained with versus without IMA occlusion was highest and most consistently positive during left IMA with LAD occlusion and during RIMA with RCA occlusion: $+0.033 \pm 0.04$ and $+0.025 \pm 0.03$.¹⁸

Permanent IMA Closure

Permanent distal IMA device occlusion is the logical consequence of the above observations collected during temporary IMA balloon occlusion. The concept had to be tested in the setting of the less frequently grafted RIMA in order not to waste an arterial graft for future use. At our institution, RIMA coronary artery bypass grafts account for 5% to 8% of all coronary grafts. In addition, the distal occlusion site at the height of the right atrium in most cases still allows the RIMA to be used as a graft artery because its length may be sufficient to be anastomized to the RCA. The site of RIMA device closure in the present study was identical to temporary balloon occlusion in the investigation by Stoller et al.¹⁸ This location was

chosen because it ought to be safely distal of and certainly not on the bifurcation of the pericardiophrenic branch. In all of the 4 cases, in whom the pericardiophrenic branch was inadvertently occluded by an IMA dissection or the device itself, no CFI increase was observed at follow-up examination. Because the IMA connects directly to the ipsilateral external iliac artery, the CFI of this vessel during ostial balloon occlusion amounts to ≈ 0.75 to 0.8 , and thus, an effect, though a lower one, on coronary CFI could also be expected in case of ostial as opposed to distal IMA device occlusion. Certainly, this functional connection of the IMA between the upper and lower extremities is primarily responsible for the safety of the procedure in our study population; the risk of tissue necrosis in the RIMA-dependent territory is most likely low, which can also be expected, because no IMA side branches are affected by IMA device closure as opposed to IMA bypass grafting.

The amount of CFI increase in response to permanent RIMA occlusion observed in this study exceeds the above described $+0.025$ during temporary occlusion by a factor of 2.7 ($+0.067 \pm 0.094$). In (an informal) comparison to other, clinically tested coronary arteriogenic treatment options, such as granulocyte-macrophage colony-stimulating factor,⁴⁵ granulocyte colony-stimulating factor,⁴⁶ ivabradine,⁴⁷ a 3-month physical exercise training,⁴⁸ and 90 hours of external counterpulsation,²⁷ permanent right IMA occlusion reached the largest CFI increase. The intraindividual comparison of CFI change between the right and left coronary territory in response to RIMA closure showed no effect on LCA CFI, the fact of which is in agreement with the ipsilateral anatomic connection between the IMA and the coronary circulation. The plausibility of the primary end point results (CFI) is enhanced by their coherence with the study's secondary end points. The effect of RIMA device closure on CFI of the RCA is reflected by a decrease in functional stenosis severity, that is, an increased FFR in the absence of direct RCA intervention; RCA PCI was performed only after follow-up end point measurements. Finally, IC ECG signs of myocardial ischemia during the 1-minute ostial RCA occlusion were quantitatively diminished at follow-up examination, and there was a trend toward fewer events of angina pectoris during the same procedure.

Study Limitations

This conceptual and feasibility study of permanent RIMA closure was not a controlled trial, with randomized allocation to device closure or no closure. Thus, the results of this study should be confirmed in a larger, randomized controlled trial, possibly with a sham-control design and the presently used surrogate, as well as clinical end-points. In the above context, the important goal of technical feasibility and initial safety of the procedure could be determined more swiftly than by selecting a controlled study design. IMA device closure may, theoretically, carry a risk for ischemia in the dependent territories. None of our patients reported symptoms associable with IMA closure during the 6 weeks of follow-up or later. In comparison to the surgical use of an IMA for bypass grafting, IMA device occlusion does not affect IMA side branches by ligation. The RIMA was not entirely occluded at follow-up in 22% of the patients. Because this was a situation more likely favoring the null hypothesis than that of CFI augmentation,

it rather supports than weakens the study findings. LCA PCI was not deferred in all, but only in 33 patients. In theory, LCA revascularization on its own could have augmented RCA CFI in this minority of patients. A subanalysis of the population with total PCI deferral ($n=33$) revealed effects of RIMA closure, consistent with those of the entire study cohort.

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Disclosures

None.

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Effect of Permanent Right Internal Mammary Artery Closure on Coronary Collateral Function and Myocardial Ischemia

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3.3 Project III

Effects of Coronary Sinus Occlusion on Myocardial Ischaemia in Humans: Role of Coronary Collateral Function

The third project was a clinical study aimed at determining the role of coronary collaterals in the effect of intermittent coronary sinus occlusion on myocardial ischemia.

My contributions were parts of the conception and design of the project, acquiring, analyzing and interpreting the data, assisting in statistical analysis and making critical revision of the manuscript for important intellectual content.

The paper was published in *Heart* in January 2013, journal ranking was #10 according to impact factor and #22 according to SCImago Journal Rank (SJR)[89] in the year of publication in Cardiology and Cardiovascular Medicine.

ORIGINAL ARTICLE

Effects of coronary sinus occlusion on myocardial ischaemia in humans: role of coronary collateral function

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ABSTRACT

Objective This study tested the hypotheses that intermittent coronary sinus occlusion (iCSO) reduces myocardial ischaemia, and that the amount of ischaemia reduction is related to coronary collateral function.

Design Prospective case-control study with intraindividual comparison of myocardial ischaemia during two 2-min coronary artery balloon occlusions with and without simultaneous iCSO by a balloon-tipped catheter.

Setting University Hospital.

Patients 35 patients with chronic stable coronary artery disease.

Intervention 2-min iCSO.

Main outcome measures Myocardial ischaemia as assessed by intracoronary (i.c.) ECG ST shift at 2 min of coronary artery balloon occlusion. Collateral flow index (CFI) without iCSO, that is, the ratio between mean distal coronary occlusive (P_{occl}) and mean aortic pressure (P_{ao}) both minus central venous pressure.

Results I.c. ECG ST segment shift (elevation in all) at the end of the procedure with iCSO versus without iCSO was 1.33 ± 1.25 mV versus 1.85 ± 1.45 mV, $p < 0.0001$. Regression analysis showed that the degree of i.c. ECG ST shift reduction during iCSO was related to CFI, best fitting a Lorentzian function ($r^2 = 0.61$). Ischaemia reduction with iCSO was greatest at a CFI of 0.05–0.20, whereas in the low and high CFI range the effect of iCSO was absent.

Conclusions iCSO reduces myocardial ischaemia in patients with chronic coronary artery disease. Ischaemia reduction by iCSO depends on coronary collateral function. A minimal degree of collateral function is necessary to render iCSO effective. iCSO cannot manifest an effect when collateral function prevents ischaemia in the first place.

ClinicalTrials.gov Identifier: NCT01625832.

INTRODUCTION

Myocardial infarct size is the main determinant of outcome following acute coronary artery occlusion.¹ It is the product of coronary occlusion time, the lack of collateral supply to the ischaemic territory, the size of the area at risk for myocardial necrosis, the absence of preconditioning ischaemic episodes prior to the occlusion, and the myocardial oxygen consumption during occlusion (the product of heart rate, contractility and ventricular wall stress).^{2–3} The amount of ECG ST segment elevation as obtained during coronary occlusion is a well known and

accurate surrogate marker for infarct size.⁴ Heart rate and myocardial contractility reduction by β -blockers have been used for decades as a measure to limit infarct size. Nowadays, the therapeutic mainstay of reducing infarct size is to confine coronary occlusion time by primary percutaneous coronary intervention (PCI). In approximately one-third of the patients with coronary artery disease (CAD), infarct size is effectively limited by a pre-existing collateral supply to the area at risk sufficient to prevent ischaemia in the event of acute coronary occlusion.⁵ In the other two-thirds of CAD patients, the time window between coronary occlusion and completion of collateral growth beyond functional recruitment is too narrow for myocardial salvage.⁶ Theoretically, reduction of the area at risk could be imagined as a means to limit infarct size in the context of its close and inverse relationship to collateral supply. In such a scenario, the area at risk would not be expected to be reduced in the absence of minimally functional anastomoses between the ischaemic and non-ischaemic territory.

In this context, coronary sinus occlusion (CSO) can be imagined to reduce ischaemic myocardium at risk for necrosis by retroperfusion, and its collateral supply has been hypothesized but not tested to be a crucial element in the action of augmented coronary venous back pressure.^{7–8} However in patients with CAD, the effect of CSO on myocardial ischaemia has not been directly examined,^{9–10} and the role of collaterals in transmitting regionally unbalanced back pressure augmentation, thereby altering adjacent area at risk sizes has not been studied so far. Therefore, the present investigation in patients with chronic stable CAD tested the hypotheses that intermittent CSO (iCSO) reduces the amount of myocardial ischaemia as quantified by intracoronary (i.c.) ECG ST segment elevation during a 2-min coronary occlusion, and that the decrease of ischaemia is dependent on the amount of collateral supply to the ischaemic territory with no effect in the absence of any and in the presence of abundant collateral supply.

METHODS

Patients and study design

Thirty-five patients with chronic stable one-vessel to three-vessel CAD were included in the study. Coronary angiography was performed for diagnostic purposes in the context of chest pain. Criteria for study inclusion were as follows: (1) no previous

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Q-wave myocardial infarction in the myocardial area undergoing temporary ischaemia, (2) no baseline ECG ST segment abnormalities and (3) absence of acute myocardial infarction or unstable angina pectoris.

This was a prospective study with randomisation for the sequence of iCSO during the first or second of two 2-min coronary balloon occlusions. The rationale of the randomised coronary occlusion sequence relates to the occurrence of collateral recruitment in the context of repetitive occlusions.¹¹ The study population was divided in a group of patients who underwent iCSO first (n=17), and in one with iCSO as the second of the two 2-min occlusions (n=18). As the primary study endpoint, i.e. ECG ST segment shift (depression or elevation in mV) during the last 10 s of coronary occlusion was determined. The main secondary endpoint was collateral flow index (CFI) as obtained during the 2-min coronary occlusion without iCSO.

The study was approved by the ethics committee of the Kanton of Bern, Switzerland, and all included patients gave written informed consent to participate.

Cardiac catheterisation and coronary angiography

Patients underwent left heart catheterisation and coronary angiography for diagnostic purposes from the right femoral artery approach. Biplane left ventriculography was performed followed

by coronary angiography. Coronary artery stenoses were determined quantitatively as per cent diameter reduction using the guiding catheter for calibration. Aortic pressure was obtained via a 6F coronary artery guiding catheter. Central venous pressure (CVP=unobstructed coronary sinus pressure) was measured via the right femoral vein.

Coronary sinus intubation and occlusion

An 8F transseptal sheath was inserted into the right femoral vein and advanced to the hepatic veins. Coronary sinus intubation was performed either by direct access using the JR 5F diagnostic catheter or an AL2 5F diagnostic catheter and a hydrophilic probing guide wire. Alternatively and in most cases, the coronary sinus was intubated retrogradely using a multipurpose 6F diagnostic catheter with the hydrophilic guide wire (figure 1). After positioning the diagnostic catheter within the coronary sinus, the hydrophilic guide wire was exchanged to a non-hydrophilic long exchange guide wire, and the transseptal sheath was advanced towards and if possible slightly into the coronary sinus. The diagnostic catheter was then exchanged for a Swan Ganz 7F balloon-tipped catheter, which was placed 2–3 cm upstream of the coronary sinus entrance into the right atrium. During the study protocol, iCSO was performed at this site.

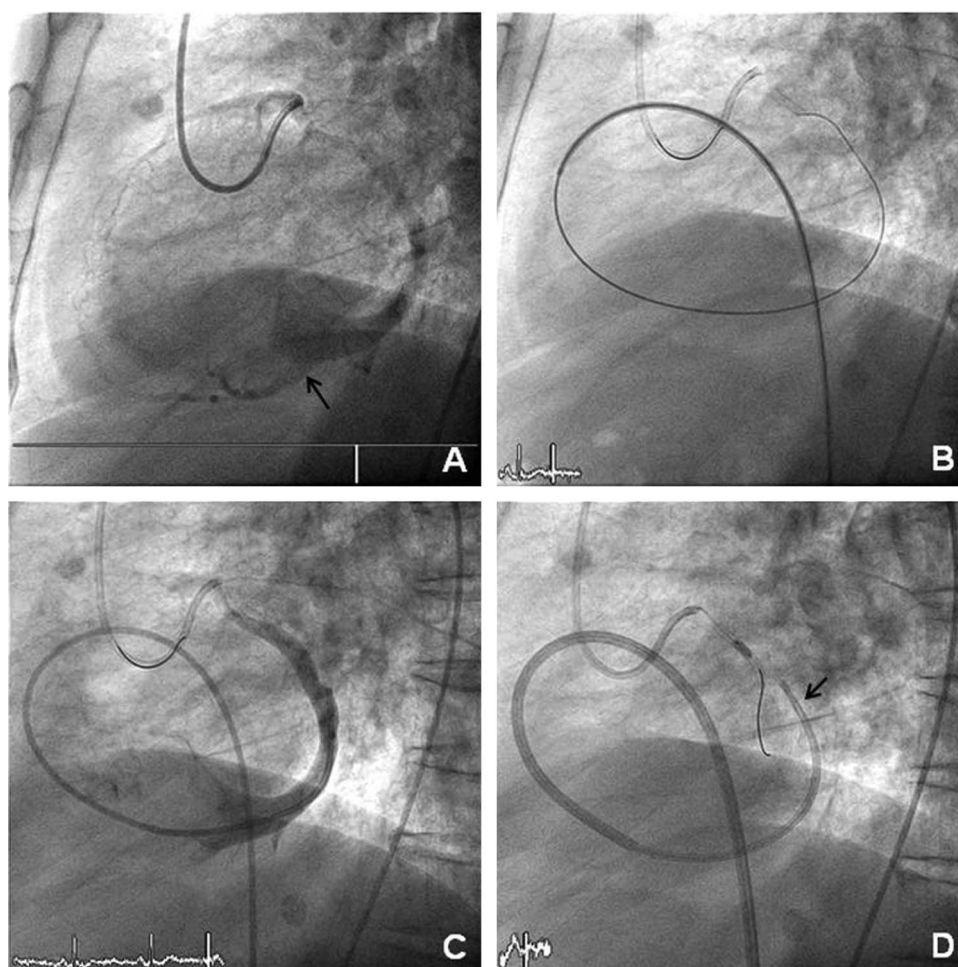
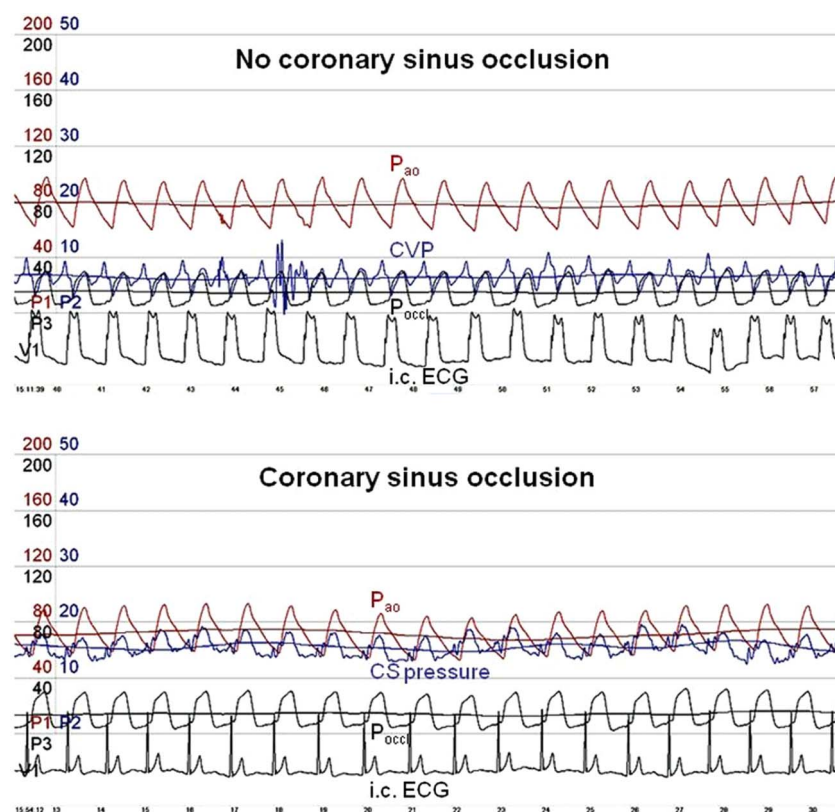


Figure 1 Panel A: Visualisation of the coronary sinus (lateral view) during the venous phase of a left coronary angiography. Far downstream, that is, shortly before the coronary sinus drainage into the right atrium, the entry of the right coronary vein into the coronary sinus is visible (arrow). Panel B: Visualisation of the hydrophilic guide wire placed in the coronary sinus. Panel C: Direct injection of contrast medium into the coronary sinus via a 6F multipurpose diagnostic catheter. Panel D: Simultaneous balloon occlusion of the proximal left circumflex coronary artery and the coronary sinus by the balloon-tipped 7F Swan Ganz catheter (arrow).

Figure 2 Upper panel: Original simultaneous recording without intermittent coronary sinus occlusion of mean and phasic aortic pressure (P_{ao} , scale: 200 mm Hg), central venous pressure (CVP, scale: 50 mm Hg), distal coronary occlusive pressure (P_{occl} , scale: 200 mm Hg) and intracoronary ECG (i.c. ECG, 0.5 mV/10 mm). Collateral flow index is calculated from mean pressure values as follows: $(P_{occl}-CVP)/(P_{ao}-CVP)$. Lower panel: Original simultaneous recording with intermittent coronary sinus occlusion of the tracings just described; coronary sinus (CS) pressure as obtained upstream of the occlusive Swan Ganz balloon catheter.



Intracoronary ECG

For the quantitative assessment of myocardial ischaemia, a unipolar i.c. ECG was obtained during coronary occlusion with and without iCSO from the angioplasty guide wire (figure 2). For that purpose, an alligator clamp was attached close to the end of the pressure sensor wire (see below) and connected to ECG lead V1.^{12 13} In addition, a three-lead surface ECG was recorded.

Coronary collateral assessment

Coronary pressure-derived (CFI, mm Hg/mm Hg; figure 2): During the coronary occlusion sequence without iCSO, collateral flow during a 2-min vascular balloon occlusion relative to normal antegrade flow through the non-occluded coronary artery was determined using coronary pressure measurements. A 0.014 inch fibre-optic pressure monitoring wire (RadiWire, Radi, Upsala, Sweden) was set at zero, calibrated, advanced through the guiding catheter and positioned distal to the site of coronary occlusion. CFI was determined by simultaneous measurements of mean aortic pressure (P_{ao} , mm Hg, via the angioplasty guiding catheter), distal coronary occlusive pressure (P_{occl} , mm Hg) and (CVP=unobstructed coronary sinus pressure): $CFI=(P_{occl}-CVP)/(P_{ao}-CVP)$ (figure 2; CFI calculation at the end of the 2-min balloon occlusion). Sensor-derived CFI measurements have been previously validated,¹⁴⁻¹⁶ and are regarded as the gold-standard for collateral assessment in humans.

Study protocol

Following diagnostic coronary angiography, the coronary sinus was intubated as described. At the start of the protocol, 5000 units of heparin were given intravenously. Two puffs of oral nitroglycerin spray were applied immediately thereafter. The angioplasty pressure sensor guide wire was positioned distal to the site of the imminent angioplasty balloon occlusion. During the entire protocol, the i.c. ECG obtained from the pressure

guide wire and a three-lead surface ECG were recorded. Simultaneous recording of P_{ao} , P_{occl} , CVP and the i.c. ECG was started before and continued throughout the 2-min balloon occlusions (figure 3). The iCSO occlusion sequence was selected at random, and accordingly, CFI was determined during the second or during the first of two 2-min occlusions. During the iCSO sequence, all the signals described above were recorded identically (figure 3). Coronary occlusion was performed using an appropriately sized angioplasty balloon. If indicated, PCI for treatment of the stenotic lesion was performed following the two study-related occlusions.

Statistical analysis

Between-group comparisons of continuous demographic, clinical, angiographic, haemodynamic, ECG and collateral flow data were performed by a two-sided unpaired Student's *t* test. A χ^2 -test (2×2 table) was used for comparison of categorical variables among the study groups. Intraindividual comparison of ECG ST segment elevations during the two coronary occlusions was performed by a paired Student's *t*-test. Curvilinear regression analysis was performed between CFI as the independent variable and i.c. ECG ST shift change without minus that with iCSO as the dependent variable; the summed least square method was applied for determining the best fit of several curvilinear functions: third and fourth order polynomial function, Gauss and Lorentz function.

RESULTS

Patient characteristics and clinical data

There were no statistically significant differences between the two groups regarding age, gender, prior myocardial infarction in a remote area, body mass index and frequency of cardiovascular risk factors as well as the use of cardiovascular drugs (table 1).

Coronary artery disease

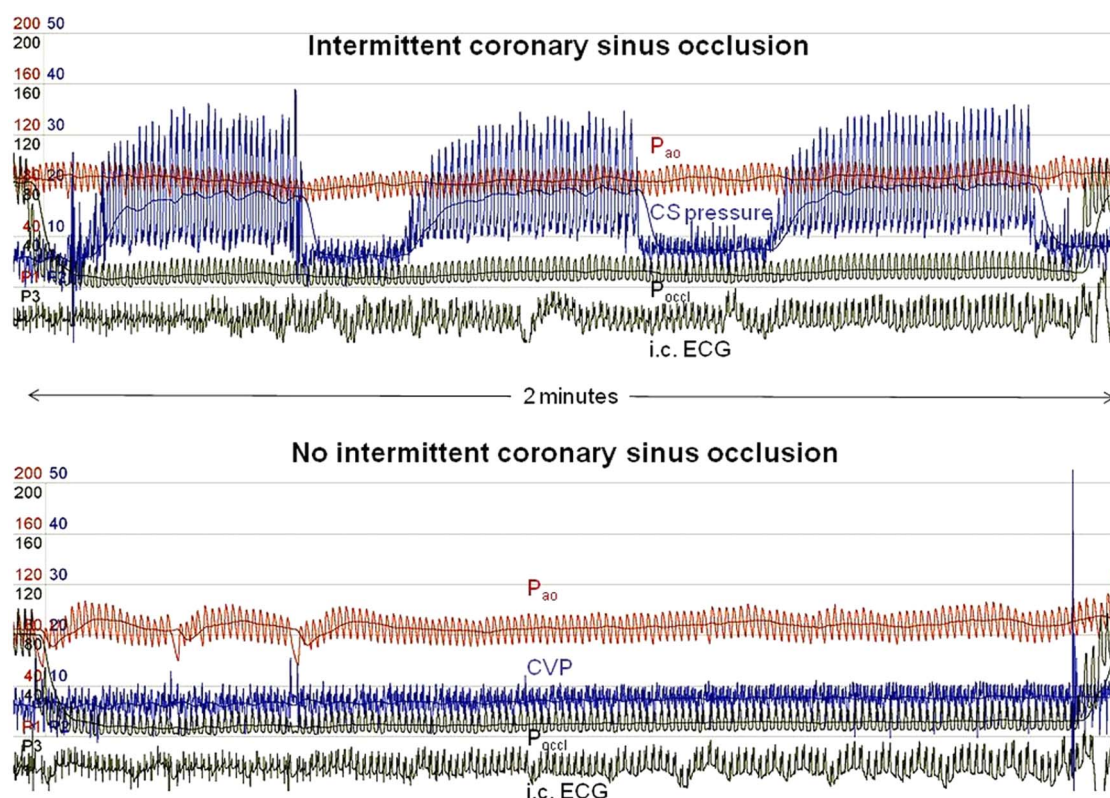


Figure 3 Upper panel: Original simultaneous recording during 2 min of coronary occlusion with intermittent coronary sinus occlusion of the following curves: mean and phasic aortic pressure (P_{ao} , scale: 200 mm Hg), coronary sinus (CS) pressure as obtained upstream of the occlusive Swan Ganz balloon catheter (scale: 50 mm Hg), distal coronary occlusive pressure (P_{occl} , scale: 200 mm Hg) and intracoronary ECG (i.c. ECG, 0.5 mV/10 mm). Lower panel: Original simultaneous recording without intermittent coronary sinus occlusion during 2 min of coronary occlusion of the following curves: mean and phasic aortic pressure (P_{ao} , scale: 200 mm Hg), central venous pressure (CVP, scale: 50 mm Hg), distal coronary occlusive pressure (P_{occl} , scale: 200 mm Hg) and intracoronary ECG (i.c. ECG, 0.5 mV/10 mm).

Coronary angiographic data

In the 35 study patients, the coronary arteries subjected to the two 2-min occlusions with and without iCSO were similarly distributed among the groups (table 2). There was no difference

between the groups in the number of coronary arteries diseased and in the vascular site of occlusion. Average per cent diameter stenosis at the occlusion site and the fractional flow reserve of the lesion were similar (table 2). The total fluoroscopy time of the entire study protocol plus PCI amounted on average to 25 min and 31 min in the two groups (range 9–56 min), respectively.

Table 1 Patient characteristics and clinical data

	Intermittent coronary sinus occlusion 1st	Intermittent coronary sinus occlusion 2nd	p Value
Number of study patients	17	18	
Age (years)	67±8	66±7	0.80
Male gender (%)	12 (71)	15 (83)	0.37
Prior myocardial infarction in remote area (%)	8 (47)	6 (33)	0.32
Body mass index (kg/m ²)	29±6	30±7	0.57
Smoking (%)	2 (12)	2 (11)	0.77
Dyslipidemia (%)	17 (100)	18 (100)	–
Hypertension (%)	16 (94)	17 (89)	0.91
Family history for coronary artery disease (%)	4 (24)	4 (22)	0.81
Diabetes mellitus (%)	3 (18)	1 (6)	0.48
Acetylsalicylic acid (%)	14 (82)	18 (100)	0.12
β-blockers (%)	8 (48)	11 (61)	0.51
Nitrates (%)	1 (6)	1 (6)	0.93
ACE inhibitor (%)	11 (61)	11 (61)	0.64
Statin (%)	12 (12)	16 (89)	0.29

Haemodynamic, myocardial ischaemia and collateral circulation data

Before the start of the study protocol, heart rate, arterial blood pressure, left ventricular ejection fraction, left ventricular end-diastolic pressure and CVP were similar between the groups (table 3).

Indicative of the action of iCSO on coronary venous back pressure (see also figure 3), coronary sinus pressure as obtained upstream of and during the phases of iCSO rose by 15 mm Hg in comparison with CVP ($p<0.0001$ for intraindividual, paired comparison), and it was not statistically different between the groups (table 3). Distal coronary occlusive pressure (P_{occl}) was elevated by 3 mm Hg during iCSO ($p=0.0437$ for intraindividual comparison); mean P_{occl} in the absence of iCSO amounted on average to approximately 20 mm Hg in both groups (table 3). Mean P_{ao} during coronary occlusion with and without iCSO was similar. Heart rate with and without iCSO was similar between the groups as well as intraindividually. I.c. ECG ST shift at 2 min of coronary occlusion manifested as ST elevation in all measurements, and it amounted to approximately 1.5 mV in the group with iCSO 1st, and to approximately 1.2 mV in

Table 2 Coronary angiographic data

	Intermittent coronary sinus occlusion 1st	Intermittent coronary sinus occlusion 2nd	p Value
Number of study patients	17	18	
Vessel undergoing occlusion			0.72
Left anterior descending artery (%)	9 (52)	8 (45)	
Left circumflex coronary artery (%)	4 (24)	4 (22)	
Right coronary artery (%)	4 (24)	6 (33)	
Number of vessels diseased			0.95
1 (%)	6 (35)	6 (33)	
2 (%)	4 (24)	4 (22)	
3 (%)	7 (41)	8 (45)	
Site of occlusion			0.23
Proximal segment (%)	17 (100)	15 (83)	
Mid-segment (%)	0	3 (17)	
% diameter stenosis at occlusion site	74±24	70±23	0.63
Fractional flow reserve (mm Hg/mm Hg)	0.73±0.16	0.76±0.17	0.66
Total fluoroscopy time (min)	25±11	31±11	0.12

the group with iCSO 2nd (table 3). Figure 4 shows the overall difference in the i.c. ECG ST shift (without minus with iCSO) between the two coronary occlusions. It was significantly less in the group with iCSO 1st, that is, the group without collateral recruitment before iCSO, than in the group with iCSO 2nd (table 3 and figure 5). Accordingly and indicative of absent and present collateral recruitment in the group with iCSO 1st and iCSO 2nd, respectively, CFI at 1 min and at 2 min of coronary occlusion was 0.132 ± 0.130 , respectively 0.130 ± 0.115 ($p=0.82$ for paired comparison) in the former group, and 0.109 ± 0.126 , respectively 0.123 ± 0.127 ($p=0.0485$) in the latter group. Figure 6 illustrates

that a decrease of i.c. ECG ST shift (maximum=2.14 mV, 95% CI=1.52 to 2.75 mV) in response to iCSO during coronary occlusion occurred at a CFI between approximately 0.05 and 0.20 (centreline of the fitted curve=0.108).

DISCUSSION

In humans with chronic stable CAD, iCSO diminishes myocardial ischaemia during coronary occlusion. The amount of ischaemia reduction during two 2-min coronary occlusions is less pronounced if iCSO is applied during the first versus the second occlusion, the latter of which goes along with recruitment of collateral function. Myocardial ischaemia is not diminished by iCSO in the presence of collateral flow sufficient to prevent it in the first place as well as in patients with poor collateral function.

Coronary sinus occlusion: data from the literature

The concept of venous retroperfusion as a way of delivering nutrients to a coronary artery territory at risk for infarction had been already introduced by Pratt at the end of the 19th century.¹⁷ The same principle led the surgeons to perform coronary venous bypass grafting as an arterial revascularisation procedure, and almost 30 years ago, CSO was introduced to provide retroperfusion by transient augmentation of coronary venous pressure.^{7–8} Subsequently, the vast majority of the studies on the topic has been performed in approximately 220 dogs and pigs undergoing acute coronary artery ligation.¹⁸ An infarct size reduction between 29–39% has been observed depending on whether iCSO alone or iCSO plus retroperfusion of arterialised blood was applied (no statistical difference between the effect of the two methods).¹⁸

Notwithstanding the high consistency of the effect of iCSO on infarct size irrespective of the animal model, the concept has been evaluated during the last three decades in only 30 patients with CAD undergoing coronary bypass grafting,^{9–19} in 34 patients with ECG ST elevation myocardial infarction undergoing thrombolysis¹⁰ and in 15 patients with chronic stable CAD receiving a coronary sinus reducer stent for the treatment of

Table 3 Haemodynamic, myocardial ischaemia and coronary collateral circulation data

	Intermittent coronary sinus occlusion 1st	Intermittent coronary sinus occlusion 2nd	p Value
Heart rate (beats/min)	78±11	73±20	0.39
Systolic blood pressure (mm Hg)	137±31	133±25	0.69
Diastolic blood pressure (mm Hg)	68±19	70±11	0.68
LV ejection fraction (%)	58±9	63±3	0.0138
LV end-diastolic pressure (mm Hg)	13±7	13±8	0.85
Central venous pressure (mm Hg)	8±4	8±4	0.62
Myocardial ischaemia and collateral circulation			
Coronary sinus pressure during iCSO (mm Hg)	22±10	23±8	0.75
P _{occl} during iCSO (mm Hg)	23±10	21±11	0.40
P _{ao} during iCSO (mm Hg)	84±26	90±23	0.53
P _{occl} without iCSO (mm Hg)	20±9	19±12	0.73
P _{ao} without iCSO (mm Hg)	89±23	89±22	0.96
Heart rate during iCSO (beats/min)	71±10	65±18	0.28
Heart rate without iCSO (during CFI; beats/min)	70±13	69±19	0.95
I.c. ECG ST shift* at 2' of occlusion (mV)	1.526±1.418	1.154±1.088	0.39
Change of i.c. ECG ST shift at 2' occl.† (mV)	0.273±0.466	0.730±0.752	0.0409
Collateral flow index (CFI) at 2' of occlusion	0.130±0.115	0.123±0.127	0.86

*'shift' corresponded to ST elevation in all measurements.

†i.c. ECG ST shift at 2 min (2') of occlusion without minus with iCSO.

I.c., intracoronary; iCSO, intermittent coronary sinus occlusion; LV, left ventricular; P_{ao}, mean aortic pressure during coronary occlusion; P_{occl}, mean distal coronary occlusive pressure.

Coronary artery disease

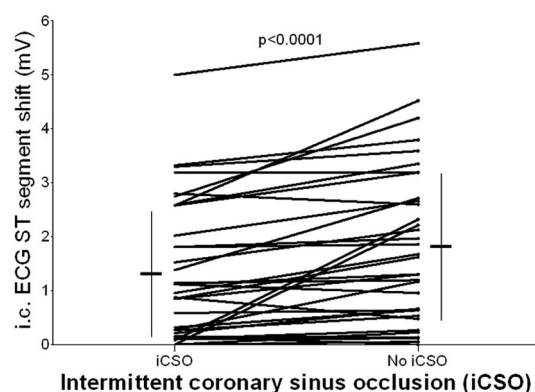


Figure 4 Individual changes of intracoronary (i.c.) ECG ST segment shift (=elevation in all cases) during the 2-min coronary occlusion with and without (horizontal axis) intermittent coronary sinus occlusion. Error bars: mean \pm SD.

refractory angina pectoris.²⁰ The study endpoints employed in the mentioned clinical trials have been left ventricular wall motion abnormalities, creatine kinase levels, major adverse cardiac events during 48 months of follow-up (as obtained in 34 patients!), and severity of angina pectoris. Though there has been a trend in these clinical studies in favour of an effect of iCSO, it has been far less consistent than in the animal studies, the fact of which may be due to their insufficient power and/or to the rather blunt study endpoints employed. At this paradoxically early stage of clinical efficacy testing of iCSO, a study design using a chronic stable 'model' of acutely and systematically induced ischaemia with a very precise surrogate measure of infarct size (i.c. ECG) is likely more adequate than the setting of acute coronary syndrome. In the present study involving 35 stable CAD patients, the overall effect of iCSO on i.c. ECG ST elevation during exactly 2 min of coronary occlusion was statistically highly relevant. However, this overall effect is only an apparent effect of iCSO, because factors aside from iCSO contributing to tolerance against ischaemia, and thus, finally smaller infarct size were active in this as in the other mentioned studies.

Mechanisms of tolerance to myocardial ischaemia

The apparent effect of iCSO found in this study is considerably larger than the real one. This is explained by pre-existing,

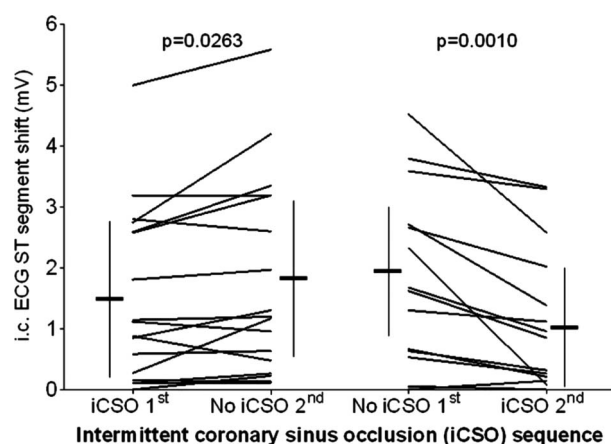


Figure 5 Individual changes of intracoronary (i.c.) ECG ST segment shift (=elevation in all cases) during the 2-min coronary occlusion with and without (horizontal axis) intermittent coronary sinus occlusion (iCSO) in the group with iCSO as the first of two coronary occlusions (left side), and in the group with iCSO as the second of two coronary occlusions (right side). Error bars: mean \pm SD.

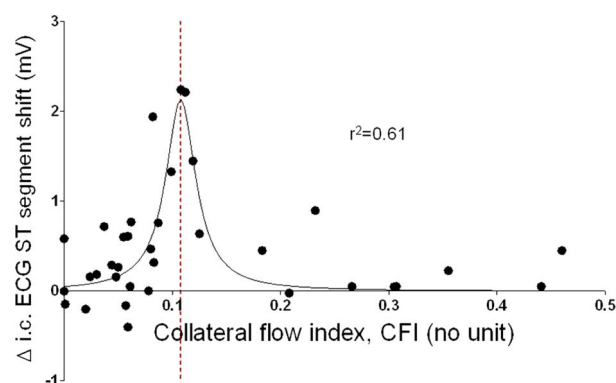


Figure 6 Curvilinear regression analysis between the change (Δ) in intracoronary (i.c.) ECG ST segment shift in response to intermittent coronary sinus occlusion (iCSO) and collateral flow index (CFI) as obtained during the 2-min coronary occlusion without iCSO. The best curve fit according to the summed least square method is a bell-shaped Lorentzian function (bold black line). The red line indicates the centreline of the function. r : regression coefficient.

constituent and by developing tolerance against myocardial ischaemia, both of which were variably present in this study. It has been documented previously that the left coronary artery territory is constitutively less tolerant to ischaemia than the right coronary artery region.¹³ Accordingly, the effect of iCSO was more pronounced when the ischaemia was induced in the former than in the latter region (maximum ST elevation reduction of approximately 1 mV vs 2.2 mV in the left anterior descending artery (LAD) region; data not shown). Possibly in the same context, Mohl *et al*¹⁰ included only patients with infarction in the LAD territory in their study. Additionally and/or alternatively, iCSO was less effective in the right than the left coronary artery because of the frequent distal anatomic right coronary artery (RCA) drainage site into the coronary sinus, which was probably not always occluded by the more upstream balloon catheter (see also figure 1).

Two factors of *developing* tolerance to ischaemia contributed to the apparent effect of iCSO, that is, ischaemic preconditioning and collateral recruitment.¹¹ In comparison with all other clinical and many experimental studies on the subject, the present one can distinguish between apparent and real effects of iCSO: the average decrease of i.c. ECG ST elevation was about 40% when iCSO was applied during the first as compared with the second of two coronary occlusions (0.27 mV vs 0.73 mV; $p=0.04$). In other words, 60% of the apparent iCSO effect was due to naturally developing tolerance against ischaemia and not to iCSO. The importance of ischaemic preconditioning in this context was probably of minor importance, since it was a constant in all patients who had been selected for coronary angiography because of angina pectoris. The principle effect of the two 2-min coronary occlusions on i.c. ECG ST elevation was likely due to recruitment of collateral function. However, this can only be deduced from the fact that there was intraindividual, significant CFI increase between 1 and 2 min of occlusion in the group randomised to iCSO during the second occlusion. In patients undergoing iCSO during the first coronary occlusion, no intraindividual collateral recruitment between 1 min and 2 min of the second occlusion could be observed. Based on a canine study by Ido *et al*,²¹ it can be speculated that collateral flow in this group was already recruited by iCSO during the first occlusion and remained, therefore, unchanged during the second.

Anti-ischaemic effect of iCSO: proposed mechanism

This possible association between collateral recruitment during the first occlusion and the effect of iCSO suggests a role of the

collateral circulation in the way how iCSO affects myocardial ischaemia. Experimental work in the porcine animal model void of coronary collaterals supports this notion by revealing no effect of iCSO on the ligation-induced fall of perfusion in the LAD from 1.5 to <0.1 ml/min/g.²² Conversely, the canine model with a coronary artery anastomotic network similar to that in humans²³ has shown an increase in the ischaemic LAD territory from 0.17–0.19 without iCSO to 0.23–0.33 ml/min/g with iCSO.^{21 24} In both the referenced canine studies, the effect of iCSO on myocardial perfusion was predominant in the penumbra and not the core of the ischaemic zone, thus indicating the transmit function of collaterals between adjacent supply areas and their role in diminishing the area at risk.

In this context and in light of the specific findings of the present study, the following mechanisms of absent or present anti-ischaemic effects of iCSO are proposed:

- ▶ There is no effect of iCSO in the high range of collateral supply to the ischaemic region sufficient to prevent ischaemia for the obvious reason that it cannot be detected even by the sensitive tool of i.e. ECG. A CFI sufficiently high to prevent ischaemia during a 1-min coronary occlusion is 0.2–0.25 and occurs in approximately 33% of the CAD population.^{5 23} In the present study, there was absent or only minimal i.e. ECG ST-elevation in the upper range of CFI.
- ▶ There is no effect of iCSO in the very low range of collateral supply to the ischaemic region, because its function is insufficient to convey the effect of augmented venous back pressure to the area at risk thereby reducing it (see below). The prevalence of CFI in the low range between 0–0.05 in a population with CAD is approximately 17%.⁵
- ▶ There is an anti-ischaemic effect of iCSO in the range of CFI (as obtained in the *absence* of iCSO) between 0.05–0.2. The collateral pathways between the non-ischaemic and the ischaemic region transmit the regionally unbalanced venous back pressure induced by iCSO. The venous back pressure as applied in the coronary sinus is regionally balanced in the venous but not in the vascular bed upstream of the microcirculation. Myocardial ischaemia results in two counteracting responses of the microcirculation, that is, maximal vasodilation and increased myocardial compressive forces in the context of diminished myocardial thickness with augmented ventricular wall stress. It is likely that in the presence of a large ischaemic territory as with proximal LAD occlusion, enhanced ventricular wall stress with heightened microcirculatory resistance prevails over ischaemia-induced maximal vasodilation. As a consequence, there is a regional imbalance in microvascular resistance with a downward gradient between the ischaemic and the non-ischaemic area. In turn, the venous back pressure augmentation by iCSO is able to reach the non-ischaemic microcirculation more easily than the ischaemic one, thereby increasing the microcirculatory resistance in the non-ischaemic zone. This leads to a flow diversion of arterialised blood to the ischaemic area at risk under the *necessary* but not always *sufficient* condition (see figure 6) of functionally present collateral connections originating from the non-ischaemic area.

Study limitations

As just outlined and alternatively, the prevailing consequence of ischaemia could be an initially lowered instead of heightened microcirculatory resistance, which would tip the regional balance during iCSO to a lower resistance in the non-ischaemic region, because of a better transmission of the increased back pressure to

the ischaemic bed. In this scenario, a steal phenomenon of blood via collaterals away from the ischaemic to the non-ischaemic region is conceivable, and could explain the considerable number of pro-ischaemic responses to iCSO in the CFI range around 0.05 (see figure 6). The present study was not designed and equipped to assess regional myocardial perfusion and resistance (eg, by myocardial contrast echocardiography) as part of the protocol, which would have allowed testing the validity of the proposed mechanism of action of iCSO. However in case of the LAD, the variability of the effect of iCSO on ischaemia was explained by factors other than CFI only to 10% ($r^2=0.91$ for curvilinear fit analogous to figure 6). As a consequence, the more important study limitation than that just mentioned is the low power in regard to the examined vessels RCA and left circumflex artery (LCX).

As a technical limitation, the site of iCSO was often selected too far upstream in order to gain catheter stability and not as far downstream as possible with obstruction of all venous tributaries. Thus, the far downstream entrance of the right coronary vein into the coronary sinus may have been excluded from iCSO. The long time for intubation of the coronary sinus and placement of the balloon catheter is a further technical shortcoming, which, most likely, did not affect the outcome of this study, but which would have to be substantially lowered in the setting of acute myocardial infarction.

Due to its size, the balloon-tipped 7F catheter in the coronary sinus possibly obstructed it already in the absence of iCSO. This would have, however, resulted in a smaller effect of iCSO versus no iCSO, and thus, would have counteracted the study hypothesis or would have conserved the null hypothesis.

Study implications

iCSO can be expected to have an anti-ischaemic effect in approximately half the CAD patients. Most likely and additionally, the population with an ischaemia in the RCA territory has to be subtracted from that. In the setting of acute myocardial infarction, iCSO has a potential to salvage myocardium following revascularisation of the culprit lesion by PCI. Considering the relevance of a certain degree of collateral supply to the area at risk as a necessary condition for the effect of iCSO, the consequences of the expected fall of collateral supply in response to PCI remains uncertain. In the setting of acute myocardial infarction, the time for access to the coronary sinus and placement of a balloon catheter has to be minimised by the use of steerable catheters. Considering the costs for such equipment plus those for a customised balloon catheter capable of applying iCSO for an extended period, the net gain of the procedure for the patient has to be carefully taken into account.

Contributors MS: Data acquisition and analysis, manuscript editing; TT: Data acquisition, manuscript editing; AAK: Data acquisition, manuscript editing; SFM: Data analysis, manuscript editing; HS: Data acquisition; CS: Study concept, data acquisition and analysis, manuscript writing, responsible for the overall content of the work.

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Effects of coronary sinus occlusion on myocardial ischaemia in humans: role of coronary collateral function

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3.4 Project IV

A Lumped Parameter Mathematical Model of Intermittent Coronary Sinus Occlusion: Role of Coronary Collaterals

Experimental and clinical studies, as well as pathophysiological considerations imply an important role of the coronary collateral circulation in the anti-ischemic effect of intermittent coronary sinus occlusion. In the in-vivo human model (Project III), characterization of the hemodynamics during intermittent coronary sinus occlusion was limited to easily accessible compartments of the heart. A mathematical model might therefore provide insight in compartments inaccessible to measurement. Although several models of intermittent coronary sinus occlusion have been published, the influence of the coronary collateral circulation has not been clearly defined. Therefore, the aim of this project was to develop a mathematical model of intermittent coronary sinus occlusion with a special regard to the coronary collateral circulation. The hypothesis was that the direct or indirect influence of coronary collaterals could be elucidated in a mathematical model.

As the results of this project are not yet published, the methods and results are summarized in the following sections.

3.4.1 Methods

A 0D cardiovascular model was developed consisting of three major parts: a heart, systemic vasculature and coronary circulation (Figure 3.1).[90]

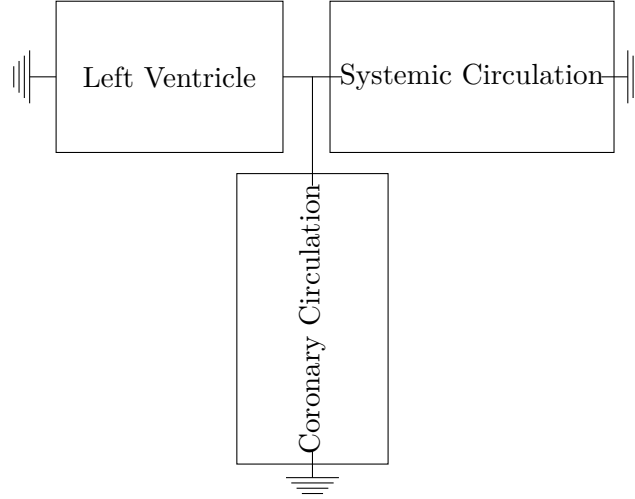


Figure 3.1: Principal structure of lumped parameter model

The systemic vasculature is represented by a four-element Windkessel [91] as a mono-compartment model. The heart is represented by an LV, modeled as a single node with a prescribed flow (see appendix 1 for details).

3.4.1.1 Coronary model

The scheme of the electrical equivalent for the coronary circulation is given in Figure 3.2. The modeled coronary circulation consists of two symmetric left coronary vascular beds, which are connected by arterial collaterals. Drainage occurs via a common pathway (the coronary sinus) and via separate non-coronary sinus pathways, representing smaller shunting veins to the ventricles (thebesian connections) and the right atrium.

Each coronary vascular bed is represented by an arterial epicardial, an intramyocardial and a venous epicardial compartment. Myocardial mass is set at 100g for each coronary vascular bed.

The arterial epicardial compartment is modeled as an Resistor-Capacitor (RC) segment, with the boundary condition of aortic pressure (p_{ao}). By increasing the epi-

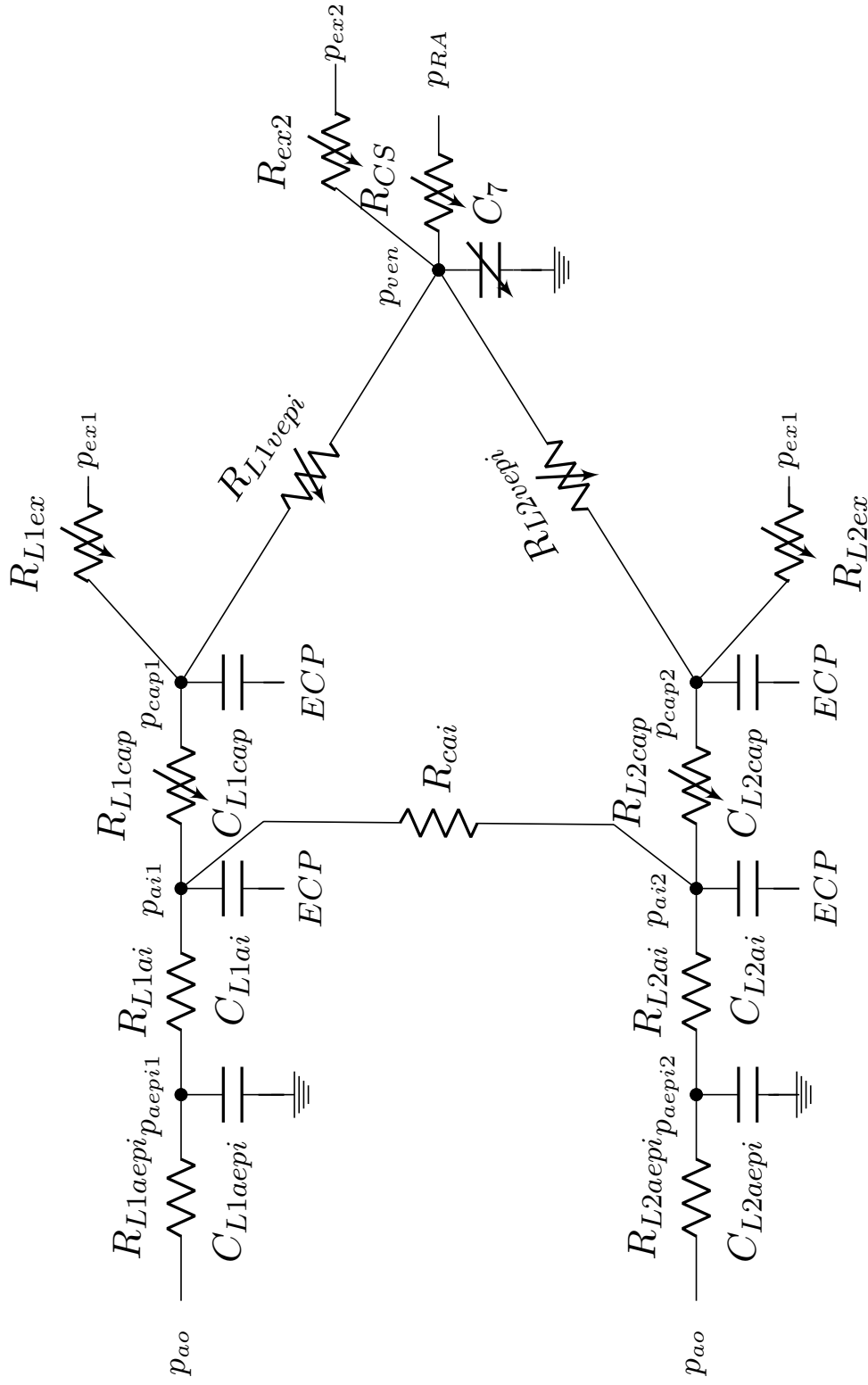


Figure 3.2: Lumped parameter model: coronary circulation.

ae , arterial epicardial. ai , arterial intramyocardial. C , capacitance. cai , collateral on arterial intramyocardial level. cap , capillary. CS , coronary sinus. ex , extra outlet. ECP , extravascular compressive pressure. L , left coronary. $L1$, left coronary, first main branch. $L2$, left coronary, second main branch. p_{ao} , aortic pressure. p_{RA} , right atrial pressure. R , resistance. ve , venous epicardial.

cardial resistance element, an epicardial coronary stenosis can be simulated.

The intramyocardial compartment is represented by two RC segments, arteriolar and capillary/venular. The interaction between the intramyocardial vasculature and the myocardium is modeled similar to the intramyocardial pump model.[92] The arteriolar compartments are connected by arterial collaterals, represented by a simple resistance.

The epicardial venous compartments are each represented by an RC segment. They connect to the same outflow point, reflecting the CS, which connects to the boundary condition of right atrial pressure (p_{RA}).

Non-coronary sinus drainage via smaller shunting veins to the right atrium and thebesian veins to the left ventricle are represented by extra-outlet resistances connecting to their respective pressure boundary conditions (left ventricular pressure (LVP) and p_{RA}).

3.4.1.1.1 Extravascular compressive pressure

The interaction between the myocardium and the coronary vessel is modeled through the extravascular compressive pressure (ECP). The ECP is assumed to be determined by the LVP (as the cavity-induced extracellular pressure (CEP) [93, 94]) and myocardial contractility.[95, 93] The ECP therefore acts on the arteriolar and capillary compliance.

$$CEP = \alpha LVP \quad (3.1)$$

$$ECP = \gamma CEP \quad (3.2)$$

with $\alpha = 0.75$, reflecting a value typical of the mid- to subendocardium.[96]. To account for contractility γ was chosen as a proportionality factor, reflecting normal contractility with $\gamma = 1$ and reduced contractility with values below 1, such as during ischemia-induced dysfunction.[95]

3.4.1.1.2 Extra outlets

Non-coronary sinus drainage principally occurs through thebesian connections into the ventricles, and veins draining directly into the atria without connecting to the CS.[97]. Therefore, the model incorporated extra outlets for non-coronary sinus drainage at the capillary/venular and at the venous level. At the capillary/venular

level, the thebesian connections were modeled as simple resistances connecting to the boundary condition of LVP, given that the model represented a left coronary system. At the venous level, the veins bypassing the coronary sinus were also represented by simple resistances, but connecting to the boundary condition of p_{RA} . Constant positive pressure offsets were added to the node pressures for the pressure-flow relationship of the extra outlets. On the capillary level, this was done to account for the fact that the pressure at the site of thebesian drainage, i.e. at the inner subendocardial layer is larger than the actual node pressure. For the venous level, the pressure offset accounted for the spectrum of pressure gradients existing for the pathways originating within the myocardium, the lower bound equal to the difference between node pressure and right atrial pressure.[98]

3.4.1.1.3 Collateral connections

Connections between the two left coronary vascular beds were implemented at the arteriolar level, represented by a simple resistor.[99] Veno-venous collaterals were accounted for in the extra outlet at the venous level.[98]

3.4.1.2 Model inputs

Inputs to the system consisted of the LVP and p_{ao} (Figure 3.2), derived from a separate lumped parameter model (LPM) based on a four-element Windkessel model [91] with a prescribed left ventricular flow rate (see appendix, Figure 1, code 2 and input to code 3 for details). Right atrial pressure was set constant at 700 Pa (5.25 mmHg).

3.4.1.3 Model parameters

Initial parameters for the model were extracted from the literature. Parameters were then adapted to achieve quantitative and qualitative pressure and flow targets. The heart rate was set at 60 beats per minute, i.e. the heart cycle was 1s. Systolic duration was 0.4s, i.e. 40% of the heart cycle.

Normal perfusion

Values for resistances and compliances during normal perfusion are shown in Table 3.1, values for compartmental volumes in Table 3.2.

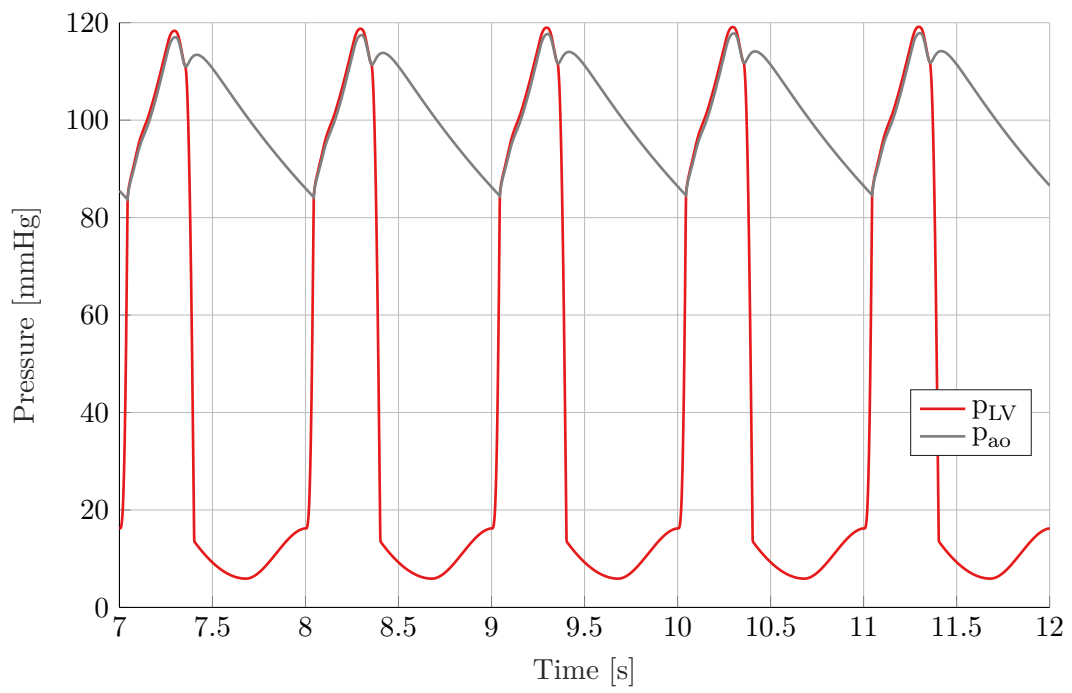


Figure 3.3: Inputs for the lumped parameter model.
 p_{LV} , left ventricular pressure. p_{ao} , aortic pressure.

Parameter	LPM	Source	Value *	Unit
Arterial epicardial compartment				
Arterial epicardial resistance	$R_{ae\pi}$	[100], adapted for stenosis	1.33×10^8	Pa s m^{-3}
Arterial epicardial compliance	$C_{ae\pi}$	[92]	3.00×10^{-11}	$\text{m}^3 \text{Pa}^{-1}$
Intramyocardial compartment				
Arteriolar resistance	R_{ai}	assumed as half of R_{cap}	1.69×10^9	Pa s m^{-3}
Arteriolar compliance	C_{ai}	[92]	1.73×10^{-10}	$\text{m}^3 \text{Pa}^{-1}$
Capillary/venular resistance	R_{cap}	inflow of 1 ml/min/g over $R_{ae\pi}$	3.44×10^9	Pa s m^{-3}
Capillary/venular compliance	C_{cap}	[98], adapted for venous pressure during coronary sinus occlusion	3.00×10^{-9}	$\text{m}^3 \text{Pa}^{-1}$
Thebesian resistance	R_{ex}	assumed	4.9×10^9	Pa s m^{-3}
Venous epicardial compartment				
Venous resistance	$R_{ve\pi}$	[98]	1.33×10^8	Pa s m^{-3}
Venous compliance	$C_{ve\pi}$	[98], adapted for venous pressure during coronary sinus occlusion	2.98×10^{-9}	$\text{m}^3 \text{Pa}^{-1}$
Coronary sinus resistance	R_{CS}	[98]	1.33×10^8	Pa s m^{-3}
Extra outlet resistance	R_{ex2}	[98], adapted for venous pressure during coronary sinus occlusion and target outflow of 10% of inflow	3.00×10^9	Pa s m^{-3}
Collaterals				
Arteriolar collateral resistance	R_{cai}	set at 5 times the arteriolar resistance[99]	8.45×10^9	Pa s m^{-3}

Table 3.1: Resistances and compliances for coronary circulation during normal perfusion

* mean over 5 heart beats

Ischemia

Coronary occlusion was modeled by increasing the epicardial resistance to 1×10^{20} Pa s m^{-3} in one coronary branch. Arteriolar resistance in the ischemic bed was set to one hundredth of normal to simulate vasodilation. Flow over the arteriolar collateral resistance was then varied in intervals of 0.05 ml/min/g, from 0-0.4 ml/min/g. A reduction in contractility was modeled by varying γ from 0-1 (equation (3.2)).

Coronary sinus occlusion

Coronary sinus occlusion was modeled by increasing the coronary sinus resistance to 1×10^{20} Pa s m^{-3} . Occlusion was released after 10 seconds.

3.4.1.4 Model equations

The following equations were introduced for the model (for parameters see Table 3.2).

3.4.1.4.1 Variable resistances

Resistances connecting to nodes with intramyocardial and venous compliances were modified to prevent emptying of compartments.

Capillary resistance

for a positive pressure gradient ($p_{ai} - p_{cap} > 0$), Figure 3.2

$$R_{cap} = R_{cap}^0 + (20 V_{ai})^{-2} \quad (3.3)$$

for a negative pressure gradient ($p_{ai} - p_{cap} < 0$), Figure 3.2

$$R_{cap} = R_{cap}^0 + (20 V_{cap})^{-2} \quad (3.4)$$

Venous epicardial resistance

for a positive pressure gradient ($p_{cap} - p_{ven} > 0$), Figure 3.2

$$R_{vepi} = R_{vepi}^0 + (20 V_{cap})^{-2} \quad (3.5)$$

for a negative pressure gradient ($p_{cap} - p_{ven} < 0$), Figure 3.2

$$R_{vepi} = R_{vepi}^0 + (20 V_{ven})^{-2} \quad (3.6)$$

Extra outlet resistance at capillary/venular level

for a positive pressure gradient ($p_{cap} - p_{Lex} > 0$), Figure 3.2

$$R_{Lex} = R_{Lex}^0 \quad (3.7)$$

for a negative pressure gradient ($p_{cap} - p_{Lex} < 0$), Figure 3.2

$$R_{Lex} = R_{Lex}^0 + (20 V_{cap})^{-2} \quad (3.8)$$

Extra outlet resistance at venous level

for a positive pressure gradient ($p_{ven} - p_{ex2} > 0$), Figure 3.2

$$R_{ex2} = R_{ex2}^0 \quad (3.9)$$

for a negative pressure gradient ($p_{ven} - p_{ex2} < 0$), Figure 3.2

$$R_{ex2} = R_{ex2}^0 + (20 V_{ven})^{-2} \quad (3.10)$$

3.4.1.4.2 Venous compliance

Venous compliance was defined as volume-dependent, according to Schreiner.[98]

$$C_{ven}(V_{ven}) = C_{ven}^0 (1 + \sigma_{ven})^{-1} \exp(-\sigma_{ven}[V_{ven}(t) - V_{ven}^0]) \quad (3.11)$$

where C_{ven} is the instantaneous venous compliance, V_{ven} the instantaneous (stressed) venous volume, C_{ven}^0 the reference venous compliance, σ_{ven} the slope of change in venous compliance and V_{ven}^0 the reference venous volume.

Variable	Parameter	Value
Arterial epicardial compartment		
V_{aepi}^0	Reference arterial epicardial volume	1.5 ml
Intramyocardial compartment		
C_{cap}^0	Reference capillary compliance	$2.66 \times 10^{-8} \text{ m}^3 \text{Pa}^{-1}$
V_{cap}^0	Reference capillary volume	1 ml
Venous epicardial compartment		
C_{ven}^0	Reference venous compliance	$2.66 \times 10^{-8} \text{ m}^3 \text{Pa}^{-1}$
σ_{ven}	Slope of change in venous compliance	0.3
V_{ven}^0	Reference venous volume	25 ml

Table 3.2: Parameter values for compartment volumes and variable compliances

3.4.1.5 Numerical solution

For the electrical analogue of the coronary circulation (Figure 3.2), a system of differential equations was formulated by setting up the balances for the pressures nodes (flow balances according to Kirchhhoff's current law) and volumes in the capacitances. The resulting system of differential equations was then solved in MATLAB (Release 2015a, The MathWorks, Inc., Natick, Massachusetts, United States) using the solver ode15s (see appendix 1 for the full code). The simulation was run for 30s. The condition of a closed coronary sinus was applied from 15s to 25s. Steady-state with the coronary sinus open was reached after 10s at the start of simulation and within 2s (2 beats) after coronary sinus release.

3.4.2 Results

3.4.2.1 Normal perfusion without coronary sinus occlusion

The lumped parameter model of the coronary circulation reproduced physiologic pressure (Figure 3.4) and flow curves (Figure 3.5) for the first left coronary branch (L1) and second left coronary branch (L2). During systole, arterial flow was retrograde due to the high values chosen for the ECP, while venous flow was highest. Conversely, arterial flow reached a maximum during early diastole and declined thereafter, in parallel to the aortic pressure.

3.4.2.2 Normal perfusion with coronary sinus occlusion

Figure 3.6 shows the increase in venous pressure during occlusion of the coronary sinus during normal perfusion. The pattern predicted by the model matched the characteristic form from the clinical and experimental trials. With release of the occlusion, baseline pressures were reached within 1-2 heart beats, also in agreement with the in-vivo observations.

Inflow reduction during CSO reached the specified target with 9.9%. Non-coronary sinus drainage without CSO was 7.6% of total outflow, slightly below the target chosen by Schreiner and colleagues.[98] As expected, the model predicted increasing retrograde flow from the venous epicardial to the lumped venular/capillary compartment and increasing non-coronary sinus drainage during CSO (Figure 3.7).

Volume during CSO increased markedly for the venous epicardial compartment, while it increased also in the lumped capillary/venular compartment. No significant changes were seen in the arteriolar and arterial epicardial compartment (Figure 3.8).

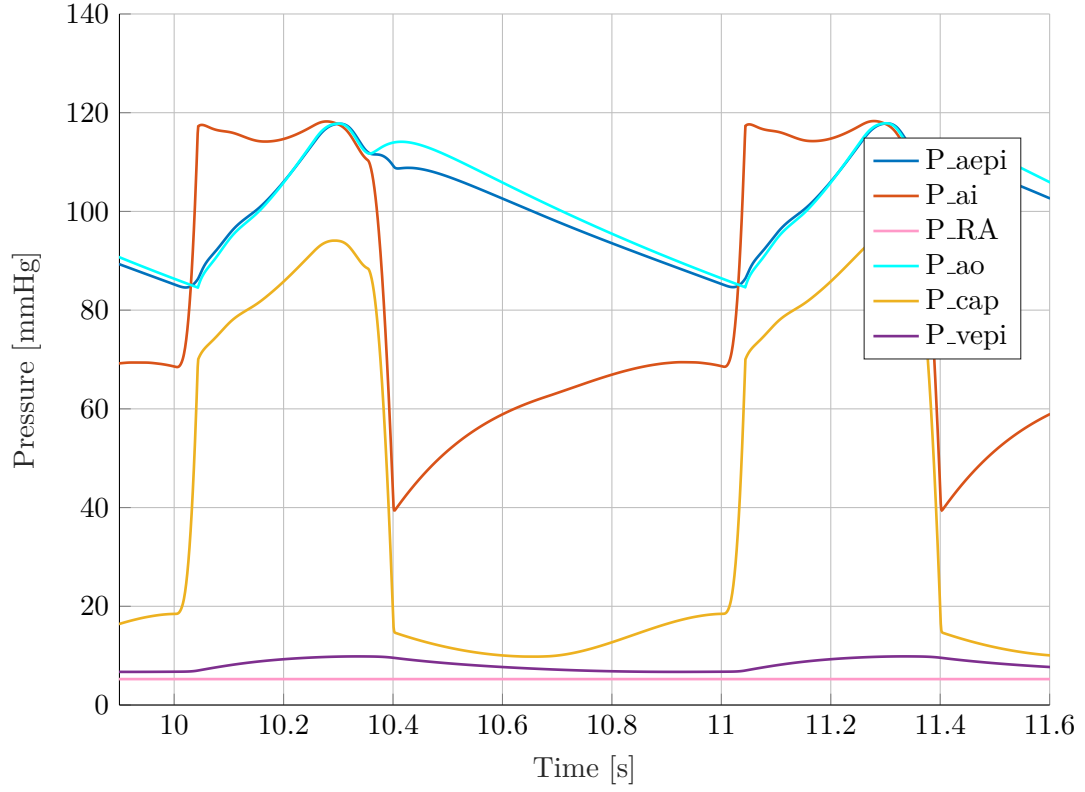


Figure 3.4: Pressure curves during normal perfusion.

Pressures shown for L1 (symmetric for L2). Systole from 10.0-10.4s, diastole from 10.4-11s.

L1, first left coronary branch. L2, second left coronary branch. p_{aepi} , arterial epicardial pressure. p_{ai} , arteriolar pressure. p_{ao} , aortic pressure. p_{cap} , capillary/venular pressure. p_{ra} , right atrial pressure. p_{vepi} , venous epicardial pressure.

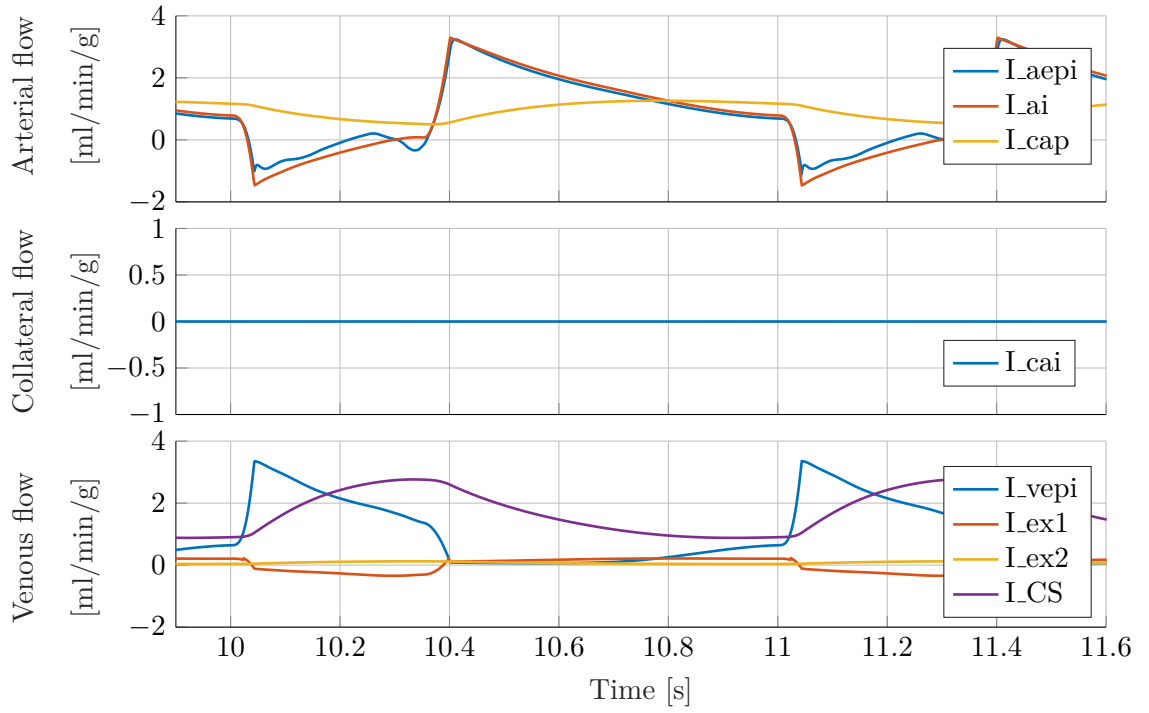


Figure 3.5: Flow curves during normal perfusion.

Flows shown for L1 (symmetric for L2). Systole from 10.0-10.4s, diastole from 10.4-11s.

L1, first left coronary branch. L2, second left coronary branch. I_{aepi} , arterial epicardial flow. I_{ai} , arteriolar flow. I_{cap} , capillary/venular flow. I_{CS} , coronary sinus flow. I_{ex1} , extra-outlet flow (thebesian veins). I_{ex2} , extra-outlet flow (non-coronary sinus). I_{vepi} , venous epicardial flow.

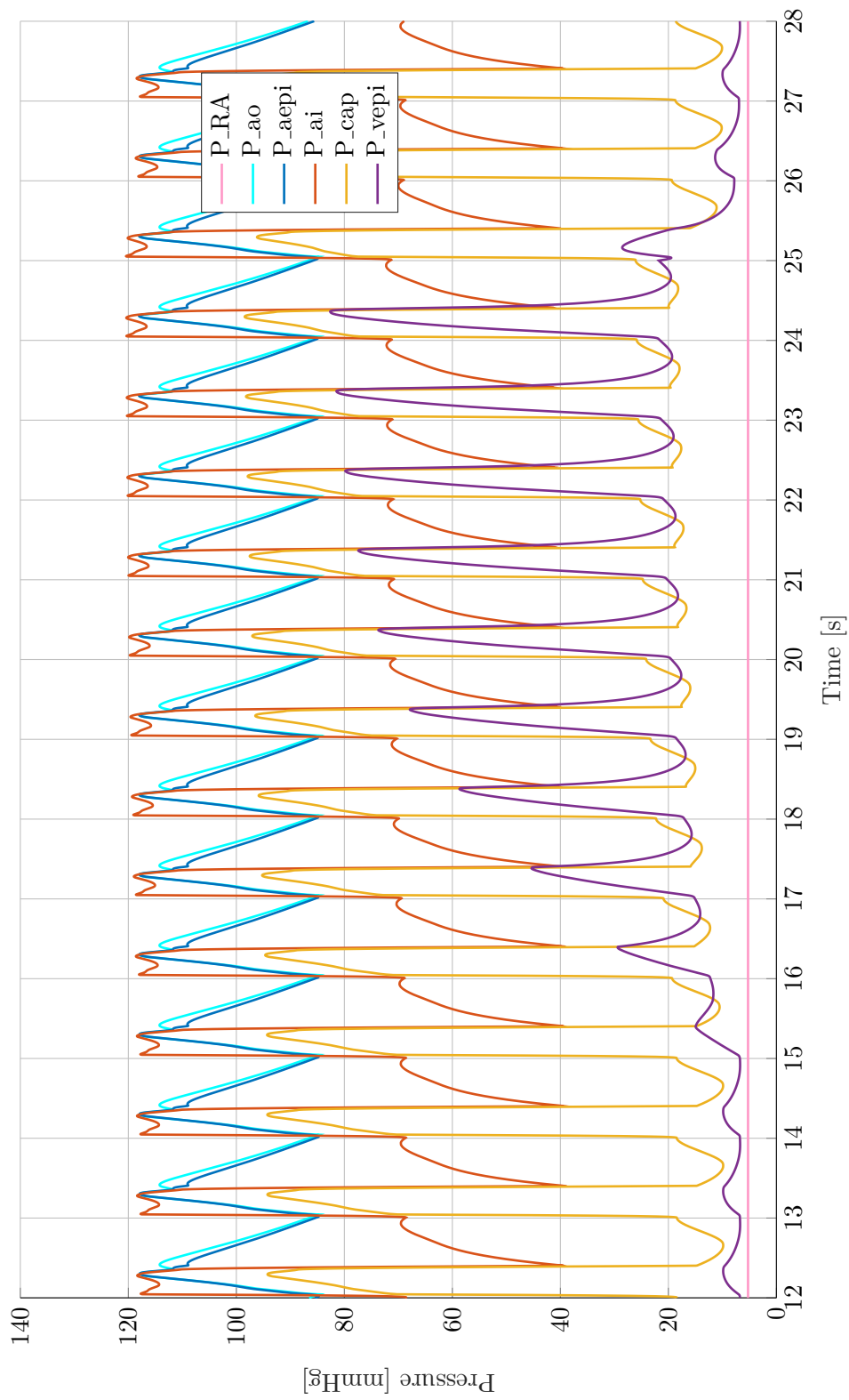


Figure 3.6: Pressure curves during normal perfusion with coronary sinus occlusion. Pressures shown for L1 (symmetric for L2).

L1, first left coronary branch. L2, second left coronary branch. p_{aepi} , arterial epicardial pressure. p_{ai} , arteriolar pressure. p_{ao} , aortic pressure. p_{cap} , capillary/venular pressure. p_{RA} , right atrial pressure. p_{vepi} , venous epicardial pressure.

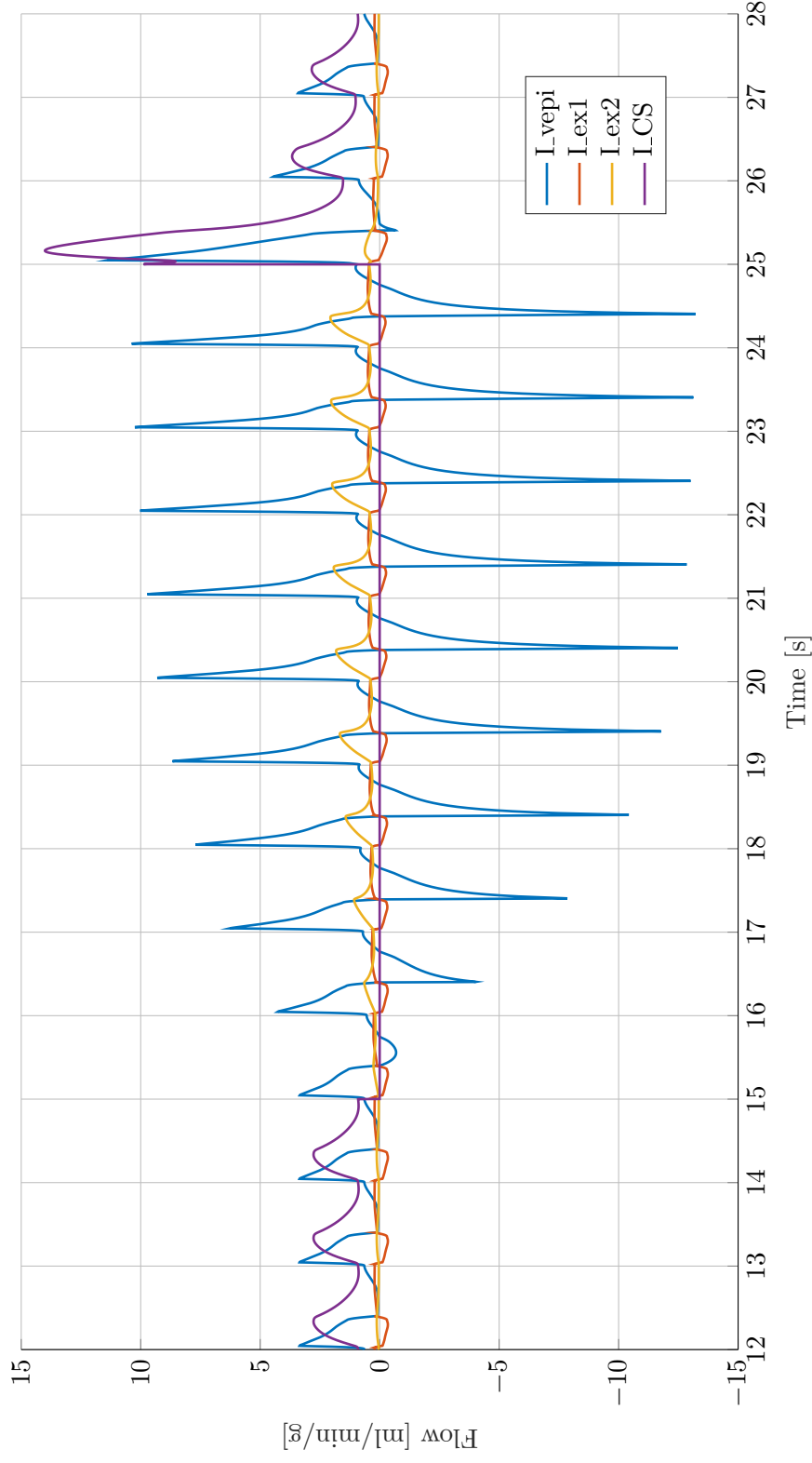


Figure 3.7: Venous flow curves during normal perfusion with coronary sinus occlusion. Coronary sinus is occluded from time 15s to 25s.

I_{ex1} , thebesian vein flow. I_{ex2} , non-coronary sinus vein flow. I_{CS} , coronary sinus outflow.
 I_{vepi} , venous epicardial flow.

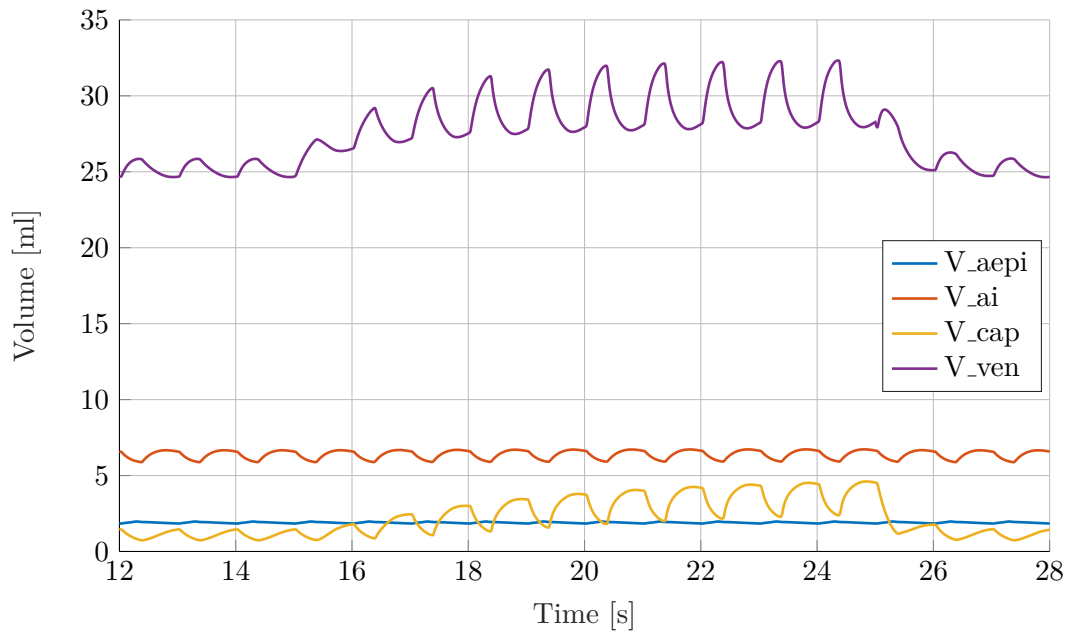


Figure 3.8: Volumes during normal perfusion with coronary sinus occlusion. Coronary sinus is occluded from 15s to 25s.

V_{aepi} , arterial epicardial volume. V_{ai} , arteriolar volume. V_{cap} , capillary/venular volume. V_{ven} , venous epicardial volume.

3.4.2.3 Ischemia without coronary sinus occlusion

During occlusion of L1, antegrade arterial epicardial flow in L1 was reduced to zero. Consequently, flow over the lumped capillary/venular compartment in L1 varied with the prescribed collateral flow (Figure 3.9). When ECP in L1 was decreased via the proportionality factor γ (Eq. (3.2)), the shape of the flow curve varied as a function of ECP (Figure 3.10), but capillary/venular flow was still a function of collateral flow (Figure 3.11), given that collateral flow was kept constant for each γ by variation of collateral resistance.

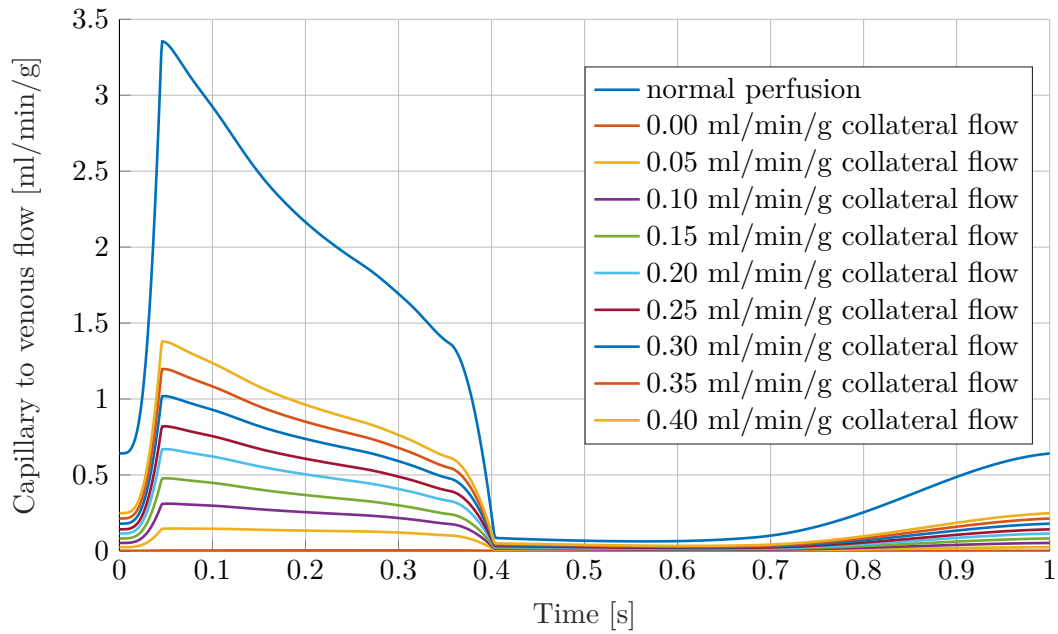


Figure 3.9: Capillary/venular flow curves during ischemia without coronary sinus occlusion as a function of collateral flow.

Single beat resolution, with collateral flow varied from zero to 0.40 ml/min/g in intervals of 0.05 ml/min/g. Normal perfusion for comparison. Extravascular compressive pressure (ECP) is set to normal.

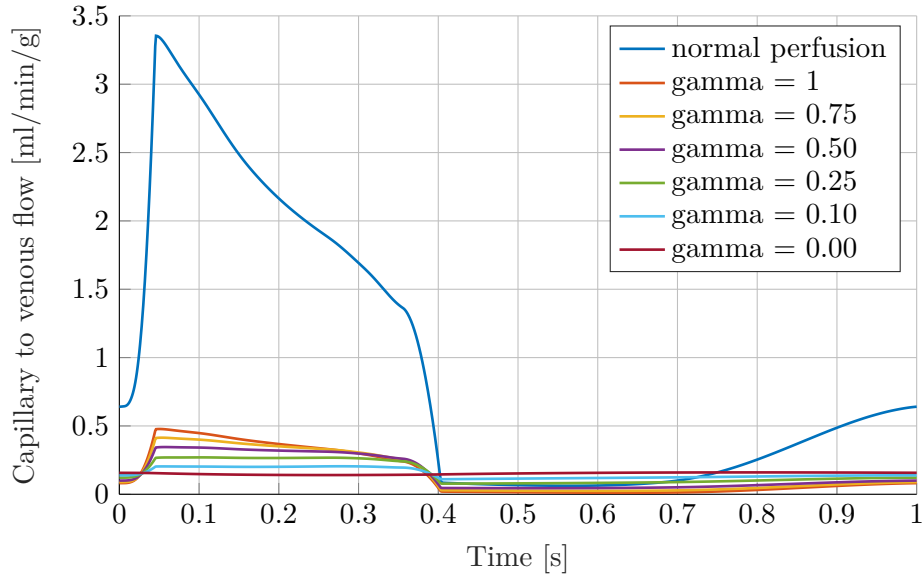


Figure 3.10: Capillary/venular flow curves during ischemia without coronary sinus occlusion as a function of ECP in L1.

Collateral flow is 0.15 ml/min/g. Normal perfusion for comparison. Flow curve varies as a function of gamma (Eq. (3.2)), the proportionality factor for ECP. ECP = extravascular compressive pressure. L1 = first left coronary branch (ischemic region).

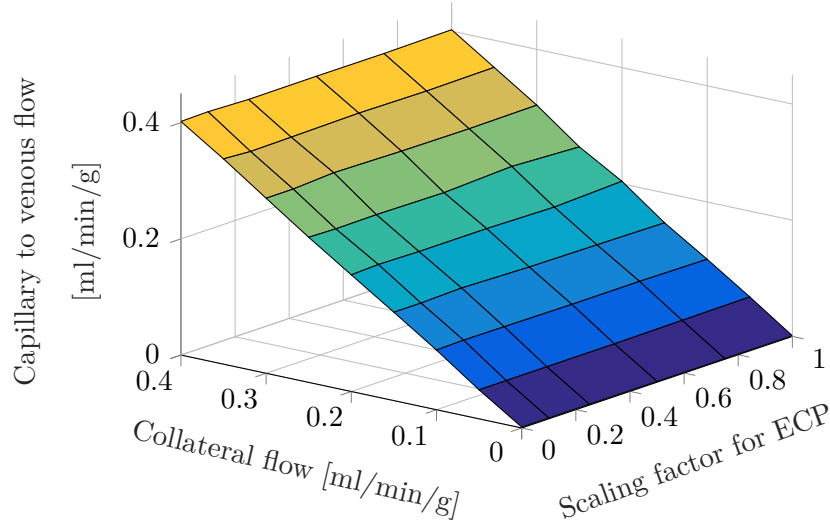


Figure 3.11: Mean capillary/venular flow during ischemia without coronary sinus occlusion as a function of ECP and collateral flow. Collateral flow is kept constant by variation of collateral resistance. ECP = extravascular compressive pressure.

3.4.2.4 Ischemia with coronary sinus occlusion

Coronary sinus occlusion reduced coronary sinus flow to zero. With CSO, flow from the capillary/venular to the venous compartment became bidirectional in both the

ischemic (L1) and non-ischemic region (L2), with retrograde flow during diastole. Retrograde flow in L1 increased with increasing duration of CSO and varied as a function of collateral flow: it increased with increasing collateral flow (Figure 3.12). For the same collateral flow, retrograde flow in L1 decreased with decreasing ECP in L1 up to $\gamma = 0.1$ and increased again with $\gamma = 0$ (Figure 3.13). Retrograde flow became apparent also during later systole with lower ECP, at γ approximately 0.25.

Collectively, mean retrograde flow during CSO increased with increasing collateral flow and was greater at higher ECP in the ischemic region L1 (Figure 3.12). Of note, with decreasing ECP in the ischemic region, retrograde flow was increasingly similar for different levels of collateral flow. In other words, lower ECP increasingly attenuated the effect of collateral flow on retrograde flow (Table 3.3).

Peak CSP (Figure 3.15) and mean CSP (Figure 3.16) also varied as a function of collateral flow and ECP, increasing with greater collateral flow and higher ECP. Collateral flow was uniformly reduced with CSO: reduction was greater with increasing collateral flow and showed a curvilinear (U-shaped) relationship with ECP (Figure 3.17), which was more marked at lower collateral flows.

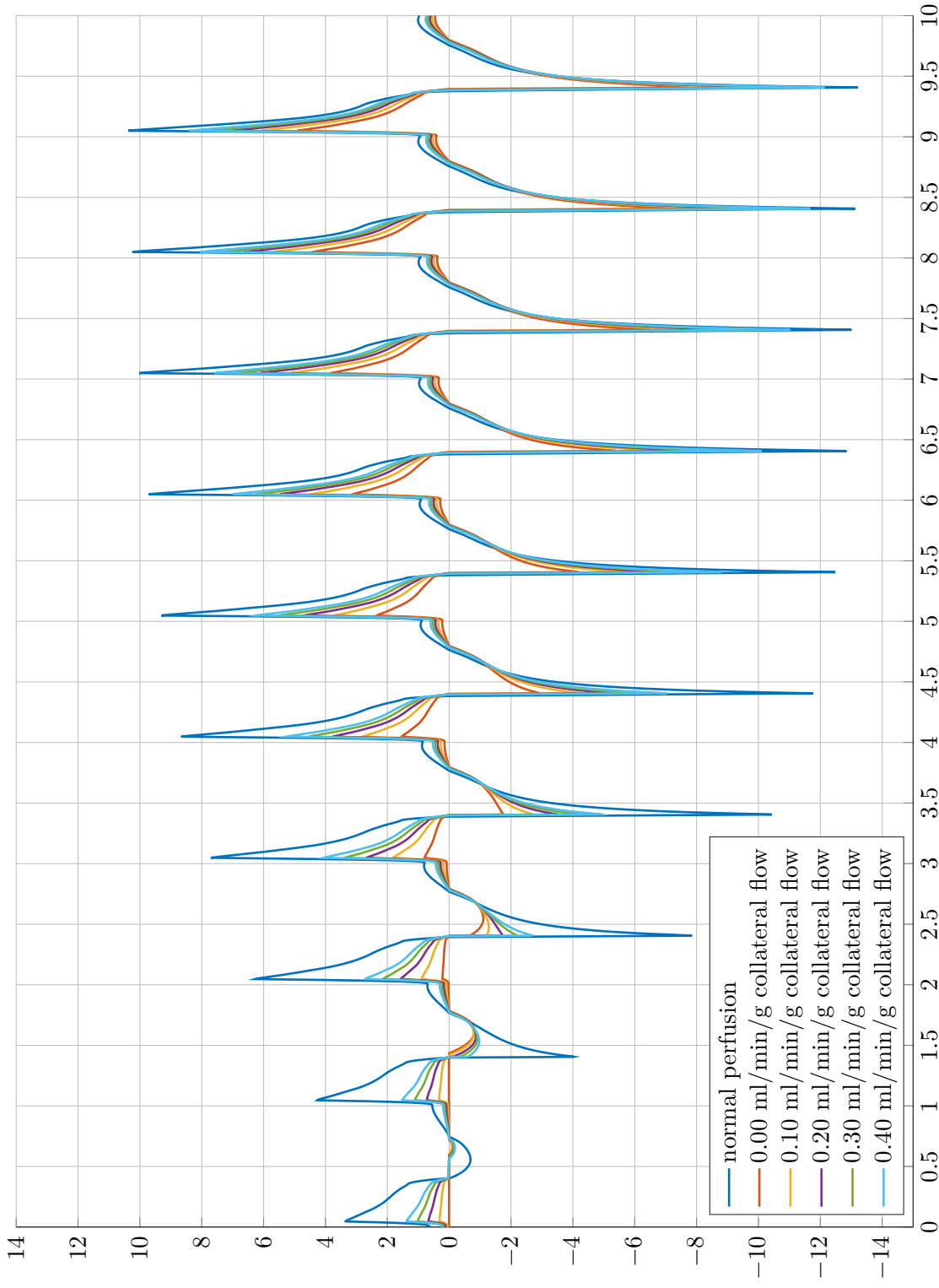


Figure 3.12: Capillary to venous flow curves during whole cycle of coronary sinus occlusion as a function of collateral flow. Normal perfusion for comparison.

ECP is constant with $\gamma = 1$. Negative values represent retrograde flow from the venous to the lumped capillary/venular compartment.

ECP = extravascular compressive pressure.

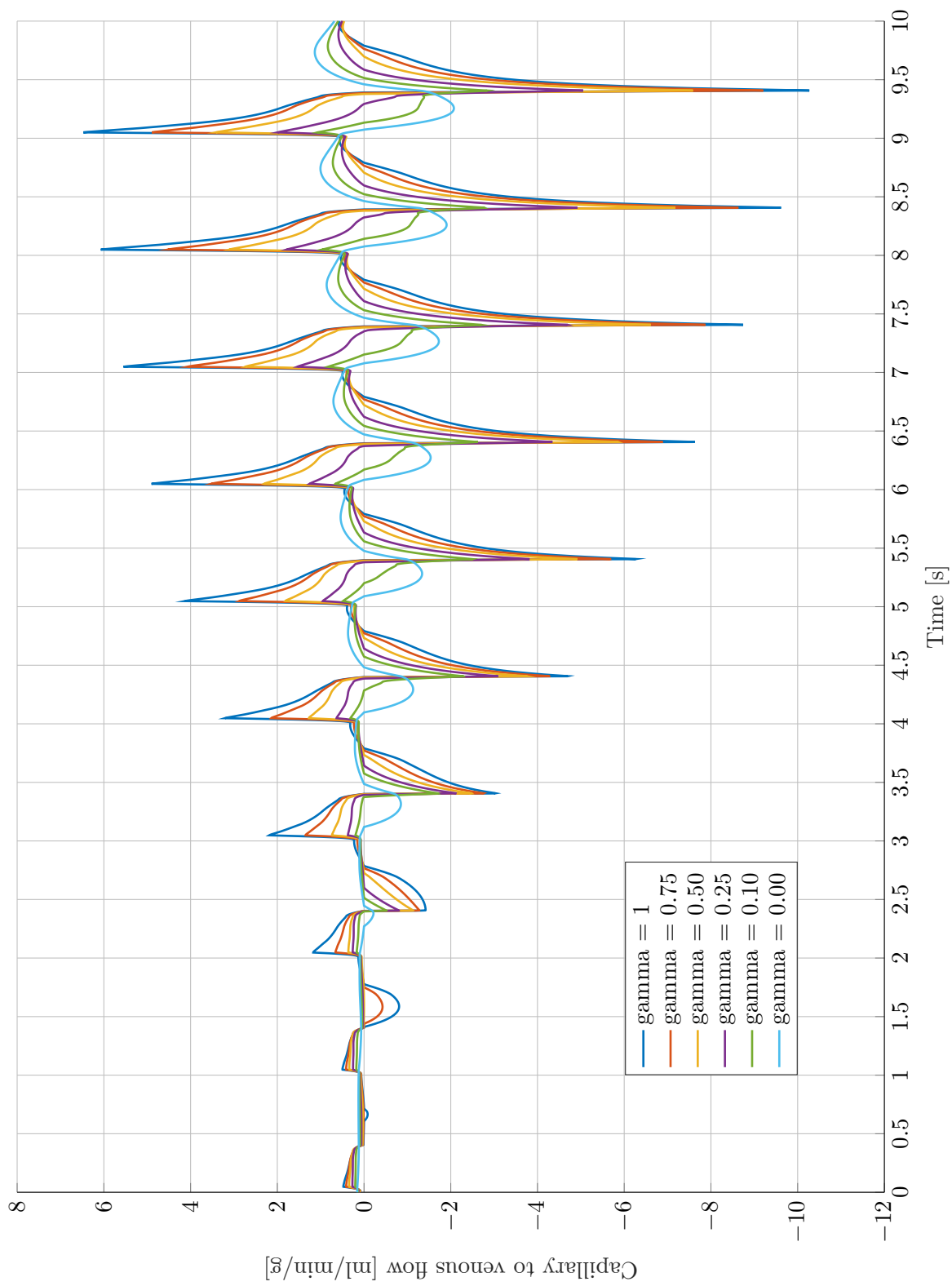


Figure 3.13: Capillary to venous flow curves during whole cycle of coronary sinus occlusion as a function of ECP. Collateral flow is set at 0.15 ml/min/g. ECP is varied with γ from zero to 1. Negative values represent retrograde flow from the venous to the lumped capillary/venular compartment.

ECP = extravascular compressive pressure, γ = proportionality factor for ECP.

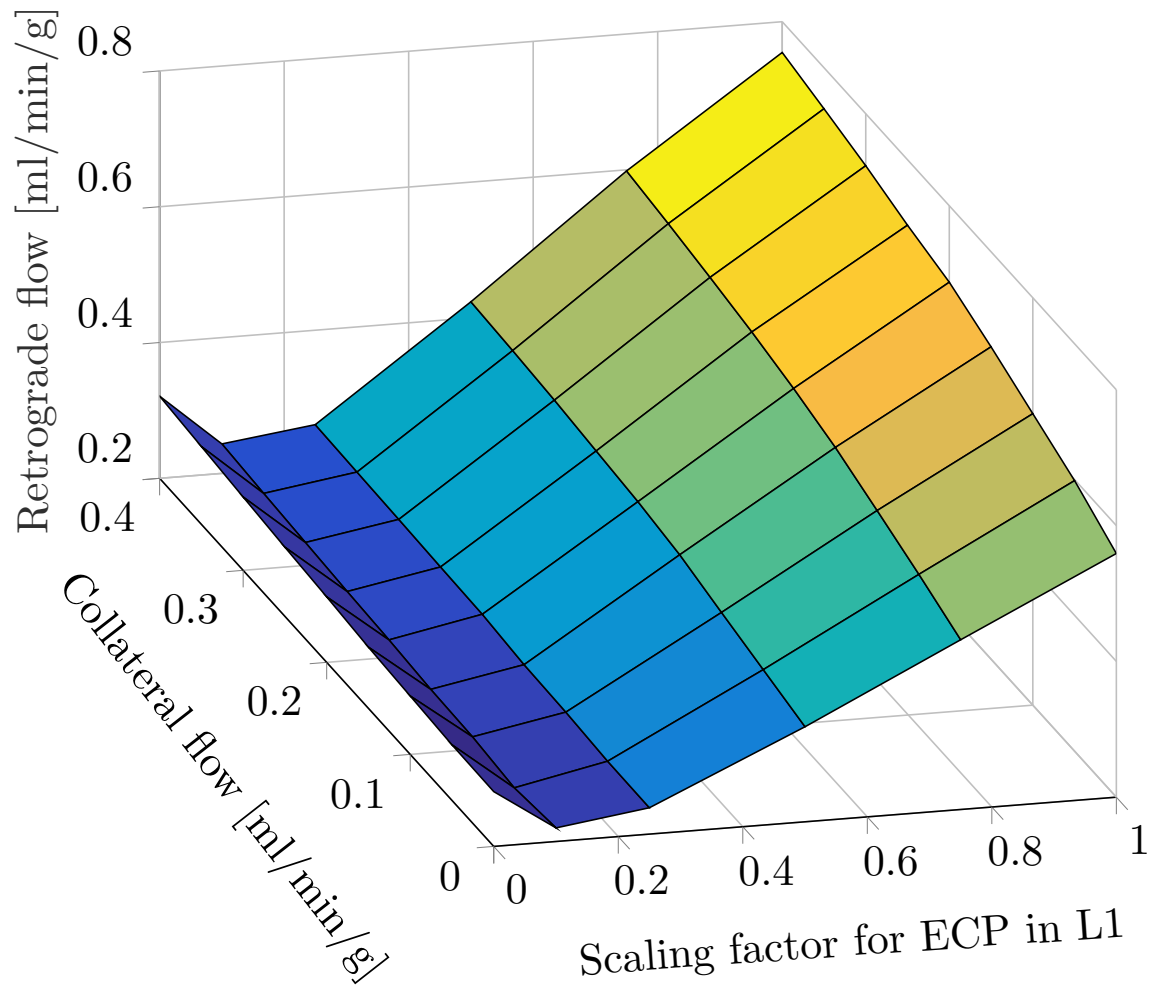


Figure 3.14: Mean flow from venous to capillary/venular compartment (retrograde flow) during ischemia with coronary sinus occlusion as function of ECP in L1 and collateral flow. Mean values over 10s of coronary sinus occlusion.

ECP = extravascular compressive pressure. L1 = first left coronary branch.

		<i>gamma</i>					
		1	0.75	0.5	0.25	0.1	0
collateral flow [ml/min/g]	0	0.56	0.45	0.34	0.24	0.22	0.28
	0.05	0.60	0.48	0.36	0.24	0.21	0.28
	0.10	0.63	0.50	0.37	0.24	0.22	0.29
	0.15	0.65	0.52	0.38	0.25	0.22	0.29
	0.20	0.69	0.55	0.40	0.25	0.23	0.30
	0.25	0.70	0.56	0.41	0.25	0.23	0.30
	0.30	0.72	0.58	0.41	0.26	0.23	0.31
	0.35	0.74	0.59	0.42	0.26	0.24	0.31
	0.40	0.75	0.60	0.42	0.26	0.24	0.32

Table 3.3: Mean retrograde flow as a function of collateral flow and ECP in L1. Mean values [ml/min/g] over whole CSO cycle of 10s.

CSO = coronary sinus occlusion, ECP = extravascular compressive pressure, gamma = proportionality factor for ECP, L1 = first left coronary branch (ischemic region).

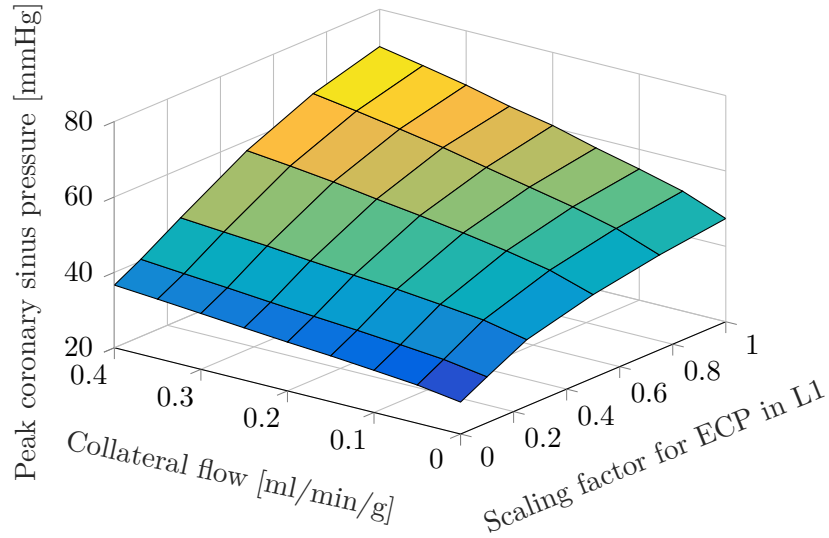


Figure 3.15: Peak coronary sinus pressures during ischemia with coronary sinus occlusion as a function of ECP in L1 and collateral flow.

ECP = extravascular compressive pressure, L1 = first left coronary branch (ischemic region).

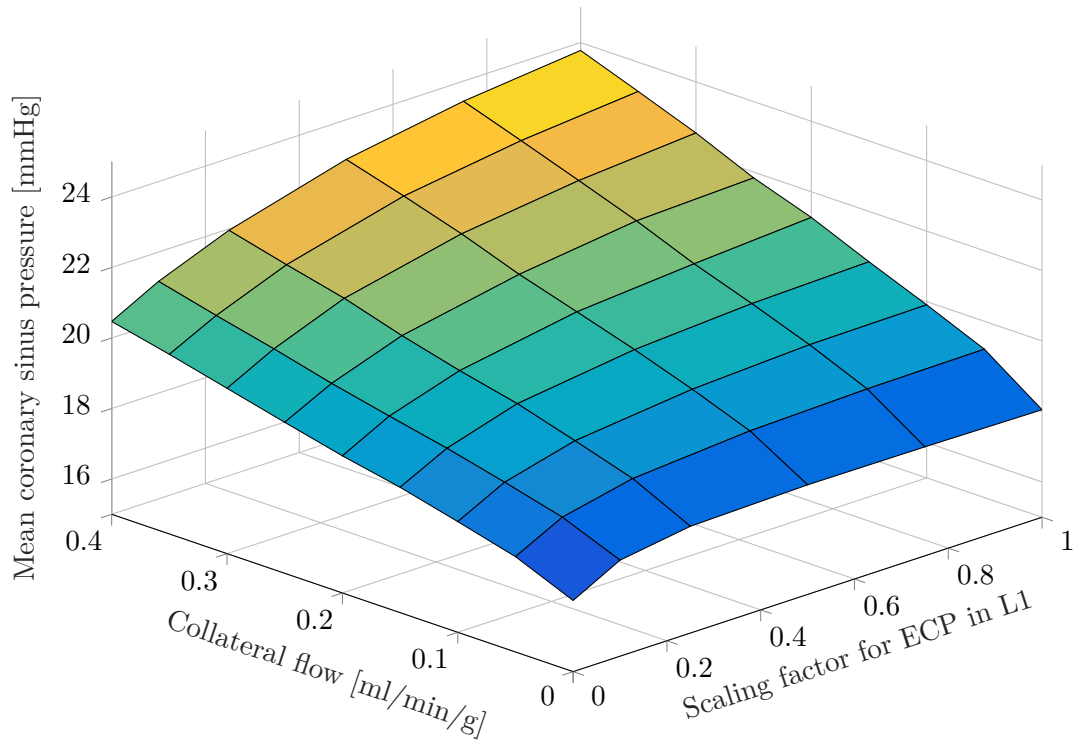


Figure 3.16: Mean coronary sinus pressures during ischemia with coronary sinus occlusion as a function of ECP in L1 and collateral flow.

ECP = extravascular compressive pressure, L1 = first left coronary branch (ischemic region).

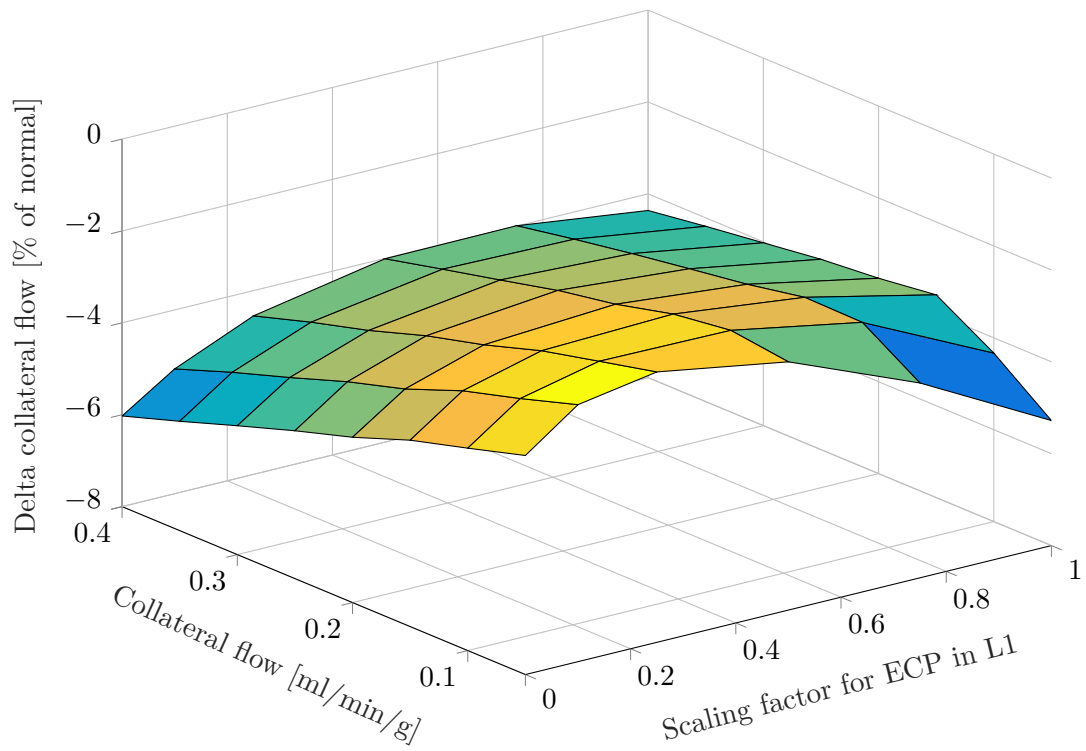


Figure 3.17: Reduction of collateral blood flow during ischemia with coronary sinus occlusion as a function of ECP in L1 and collateral flow.

Reduction in collateral blood flow expressed as percentage of collateral blood flow without coronary sinus occlusion (delta collateral flow).

ECP = extravascular compressive pressure. L1 = first left coronary branch (ischemic region).

4. Discussion and Outlook

The main aims of this study were to investigate the extracardiac coronary collateral circulation (Projects I and II) and the role of coronary collaterals in the anti-ischemic effect of CSO (Projects III and IV).

Extracardiac Collaterals

In a first-in-man study, we could demonstrate evidence for functional, ischemia-reducing collateral supply from the internal mammary artery to the coronary circulation (Project I). In the clinical study, the augmentative effect of distal IMA occlusion on collateral function and consequently a reduction in regional myocardial ischemia could be demonstrated for the ipsilateral coronary branch, ie left IMA to LAD and right IMA to RCA. In the case of the LCX, the findings were equivocal, with a variable response of collateral function to ipsi- or contralateral distal IMA occlusion. As a continuation of the preliminary trial, we could further provide evidence in favour of structural growth of anastomoses between the right IMA and the RCA in response to distal right IMA occlusion, whereas overall no effect was demonstrated on collateral function in the left coronary artery (Project II).

Clinical vs anatomic findings

The pathology studies demonstrated IMA-to-coronary anastomoses only for the RCA and LCX, but not for the LAD. Furthermore, the few angiographic case reports in vivo of IMA-to-LAD anastomoses[28, 29, 30] were documented exclusively in patients with prior heart surgery. Prior heart surgery and inflammatory conditions of the pericardium are known to cause adhesions between the pericardial layers, which might have enabled these connections to occur not primarily but secondarily.[26]. Moreover, on anatomical grounds and consistent with the pathological findings, atrial coronary

branches conceivably mediate connections between the IMA and a ventricular coronary branch via an atrial coronary branch. Most atrial coronary branches have been described to arise from the RCA and the LCX, with a minority originating from the left main coronary artery.[23] However, consistent atrial branches have not been described for the LAD. At variance with these observations, our clinical study provided evidence also for left IMA to LAD anastomoses. A possible explanation might be the methodical difference between the qualitative angiography in the pathology studies and the arguably more sensitive quantitative functional assessment in our study.

With respect to contralateral distal IMA occlusion, no effect on collateral function or regional myocardial ischemia could be detected for the LAD or the RCA, which is consistent with the findings from angiographical case reports and the pathology studies. For the LCX, CFI was higher with ipsilateral IMA balloon occlusion and trended to be higher with contralateral IMA occlusion ($p=0.08$), however, regional myocardial ischemia was not different with either ipsi- or contralateral IMA occlusion. Anatomically, however, connections to the LCX are conceivable via left atrial and also the largest atrial branch, the sinus node artery.[20] Moreover, angiographically, IMA anastomoses to the LCX from both the ipsilateral[34] and contralateral side[31] have been documented. Taken together, the findings from our clinical study are at variance with these considerations. On balance, it seems reasonable that extracardiac anastomoses to the LCX exist from both the right and the left IMA, but that the clinical study lacked in statistical power to detect their prevalence.

Promotion of extracardiac collaterals

In our first-in-man study we provided evidence for the proof of concept to promote right coronary collateral function by distal right IMA closure. Compared to other trials on the promotion of collateral function, this study method is among the first that could provide a durable promotion of collateral growth. The method could be likened to a model of physical coronary arteriogenesis,[11] although the mechanism by which the presumed augmentative effect of distal IMA closure is exerted, remains speculative. Whereas the acute effect of distal IMA occlusion by balloon in the preliminary study[70] can be interpreted as a functional recruitment of IMA-to-coronary anastomoses, [101, 102] the chronic effect by permanent distal IMA closure

in the exploratory therapeutic study can be regarded as a structural adaptation.

Prior studies necessitated recurrent application of the arteriogenic stimulus to sustain the effect of collateral growth promotion. Repetitive application of an arteriogenic treatment is, however, cumbersome,[12] dependent on patient compliance[13, 10, 12] and may have unwanted side effects.[8, 103] Comparing the effect size of the different interventions is difficult, given the differences in patient characteristics. Nevertheless, the increase in CFI attributed to a response to permanent right IMA closure ($+0.067 \pm 0.094$) is among the largest compared to other clinically tested collateral promotion trials.

The study hypothesis postulated a differential effect of right IMA closure on collateral function in the right vs the left coronary artery. Specifically, we hypothesized that right coronary collateral function would improve, whereas no change would be seen for the left coronary artery. This hypothesis was based on the study findings from the preliminary trial.

The positive study results of an augmenting effect on right coronary collateral function from right IMA closure have to be interpreted in light of a lack in randomization of the intervention. Therefore, confirmation in a randomized study design is mandatory to derive more definite conclusions regarding the efficacy of the intervention. In case of confirmation, distal right IMA closure appears most suitable as an alternative adjunct to established revascularization procedures in patient subsets with coronary lesions not amenable to conventional therapy. Mainly, this applies to patients with ischemia in the RCA territory, specifically chronic total occlusion (CTO) of that artery. Chronic total occlusions are commonly found during coronary angiography, [104] but due to lower procedural success rates and a higher complication rate compared to non-CTO interventions,[105] a conservative approach is not unusual for these lesions.[106] From an anatomical point of view, it appears reasonable that the occlusion should be situated before the sinus node artery, given that it has been implicated to mediate the extracoronary collateral connection.

Reluctance seems justified to perform distal *left* IMA occlusion as a means to improve collateral function of the LAD, given that it might preclude its utilization for CABG, where it is almost universally used. On the other hand, the practice of

bilateral IMA grafting is infrequent,[107, 108] which places less restriction on right IMA interventions in the context of arteriogenic trials. Nevertheless, given its distal position, occlusion of the IMA might not entirely exclude its use in future CABG.

Coronary Sinus Intervention

The clinical trial on intermittent CSO in patients with stable CAD was consistent with an important contribution of the coronary collateral circulation in the anti-ischemic effect of this intervention (Project III). With very low collateral function, regional myocardial ischemia during a 2-minute coronary balloon occlusion was not different with or without CSO. Similarly, an additional anti-ischemic effect of CSO was not demonstrated with high collateral function, given that signs of myocardial ischemia were practically prevented by sufficient collaterals in the first place. In comparison, in the intermediate range of collateral function, there was a pronounced effect of CSO in reducing electrocardiographic signs of ischemia.

Given the multitude of influencing factors and variables not accessible to measurement, a lumped parameter computer model was also developed.

Role of coronary collaterals: clinical vs experimental findings

In experimental trials, a reduction in myocardial infarct size by CSO was demonstrated regardless of the collateral status of the examined species. Thus, salvage of myocardium could be observed also in the pig, which is notorious for its minimal collateral circulation. A differential effect on infarct size with CSO in species with good versus poor collaterals is hampered by the heterogeneity in the study protocols.[53] Notably, key influencing factors for infarct size, such as the duration of coronary occlusion and the timing of CSO differed significantly between the experiments. A difference in effectiveness of CSO as a function of the collateral status can therefore not be drawn on the basis of the extent of infarct size reduction. However, the demonstration of infarct size in species practically devoid of arterial collaterals implicates mechanisms in reducing myocardial ischemia also functioning in the absence of coronary collaterals. In this context, the model of selective coronary vein occlusion as opposed to occlusion of the major collecting vein is instructive.

Occlusion of the CS results in an increase in CSP which is transmitted back to its tributaries, mainly, the venous branches of the left coronary arteries. Thus, the

outflow pressure is increased to both ischemic and non-ischemic regions, assuming ischemia in the territory of one of the left coronary branches. Consequently, owing to a decreased perfusion pressure in the ischemic region, the impedance to outflow may favour a redistribution of flow from the non-ischemic to the ischemic region.[78, 79] This flow redistribution could conceivably be mediated by coronary collaterals. The extent of flow redistribution would then be dependent on the size of the pre-existing collateral connections. With minute collateral connections, little capacity could be expected, whereas larger increases would be imaginable with more sizeable collaterals. The provisions to this hypothesis would for the collateral donor to originate from the left coronary artery, eg from the LCX in the case of LAD occlusion, given that the RCA is unaffected by CSO. In pigs, microsphere-measured regional myocardial blood flow in the ischemic region was practically zero and was not enhanced by CSO.[79] Measuring regional myocardial perfusion by the microsphere method equates to collateral blood flow.[84] In dogs, regional myocardial blood flow in the ischemic region was enhanced by CSO in one study in dogs.[78] However, an augmentation of collateral function by CSO was not found in other studies in dogs [63, 109, 64]. Collectively, these data indicate that collateral flow is not typically augmented by CSO.

With selective occlusion of the vein draining an ischemic region, the resulting outflow impedance is limited and will not affect drainage in non-ischemic regions.[79] In fact, an inhibitory effect on any antegrade flow in the region drained by the occluded epicardial vein is likely, given the greater restriction on outflow with more upstream vein occlusion.[79] Selective intermittent vein *occlusion* in dogs did not reduce infarct size,[83], an observation consistent with a lack of effectiveness of that method in the absence of flow diversion from non-ischemic zones. Selective vein *retroperfusion* with arterial blood, however, lead to significant reductions in infarct size compared to control.[83] In this situation, effective retroperfusion of the ischemic region is the likely mechanism of ischemia reduction. Qualitatively, it was proven by dye staining that retroperfusate injected selectively in a coronary vein reached the capillary level in ischemic (but not in non-ischemic) myocardium.[110]

The effectiveness of coronary sinus intervention (CSI) with well- vs poorly-functioning collaterals can be appreciated in comparing retroperfusion trials in pigs with the experimental findings of CSO in dogs. Retroperfusion and CSO in pigs was effective in preserving myocardial viability, but only retroperfusion at high flow rates and high

counter-pressures (80-120mmHg) was effective in restoring myocardial function.[111, 112] In contrast, CSO alone was effective in (partial) restoration of myocardial function in dogs.[113]

Role of coronary collaterals: findings from mathematical model

Several computer models of coronary sinus occlusion have been published, notably by Schreiner,[114, 115, 98, 116, 117], Neumann[118] and Beyar[119] and colleagues. The models invariably simulated a two-branch left coronary system, given the fact that the right coronary system is practically unaffected by CSO. Schreiner and Neumann and colleagues extensively investigated the modulating influence of variable myocardial squeezing on the extent of retrograde flow to the ischemic region. In their model, the squeezing pressure was set proportional to LVP and decreasing contractility was simulated by a decreasing factor of proportionality. They found myocardial squeezing to be necessary to cause effective retrograde perfusion from the venous towards the capillary compartment. Retrograde flow increased with increasing squeezing pressure, while very strong squeezing again reduced retrograde flow. On theoretical grounds, their modeling approach of contractility does not seem unreasonable, given that the interaction between the coronary vessels and the myocardium currently seems indeed best explained by the combined effect of LVP-derived interstitial pressure (CEP) and contraction-induced intramyocyte pressure (shortening-induced intracellular pressure).[93, 120] Uncertainty exists, however, for the exact contributions of the two mechanisms. It has been estimated that the effect of contractility on ECP was at least 50% of that of the LVP.[120] Consequently, although it is reasonable to assume that reduced contractility lessens retrograde flow during CSO, its relative impact remains difficult to estimate.

With one exception, the published models of CSO did not include arterial collaterals between the non-ischemic and ischemic territory. Yet, although Beyar included collaterals on the arterial level, his investigation in this respect was limited to but one level of collateral flow (10% of normal antegrade flow). Therefore, the role of different levels coronary collaterals in the anti-ischemic effect of CSO remained unexplored. With regard to a proposed augmentation of collateral flow by CSO, the model by Beyar predicted the opposite: collateral flow to the ischemic bed was reduced by CSO.

The model of this thesis provided valuable additional insight in the variables determining the effect of CSO. First of all and importantly, however, it could reproduce the salient physiologic specifics of coronary pressure and flow during ischemic and non-ischemic conditions, with the collateral circulation being an integral part of the model. Secondly, the model could reproduce quantitative and qualitative pressure and flow patterns during CSO, in particular retrograde flow during CSO and the characteristic form of venous pressure. In this respect, the model can be seen on par with prior published computer models on the subject.

With regard to the influence of myocardial squeezing on retrograde flow, this model in essence reaffirms prior findings: a decrease in contractility modeled via a reduction in ECP lead to a concomitant decrease in retrograde flow to the ischemic region. The model did not investigate stronger squeezing than the physiologically assumed. The novel finding of this computer model is the influence of the extent of collateral function on the anti-ischemic effect of CSO. The model predicted retrograde flow to the ischemic region to be positively correlated with the prescribed collateral flow. Assuming constant contractility, a modest increase in mean retrograde flow during a 10s cycle of CSO was predicted, for example a 25% increase at a collateral flow of 0.25 ml/min/g relative to no collateral function. Importantly, though, contractility in an ischemic region is reduced as a function of its remaining blood flow, in the case of total occlusion as a function of its collateral supply. Therefore, the combinations of reduced contractility and levels of collateral flow were also examined. The model predicted retrograde flow to be strongly affected by the combination of more reduced contractility with poorer collateral function compared to more preserved contractility with better collateral function. Specifically, assuming a reduction of ECP to half of normal with total ischemia (zero collateral flow), retrograde flow was 60% of that with normal contractility. Conversely, assuming preserved contractility with a collateral flow of 0.20 ml/min/g, retrograde flow was twice as high compared to the former constellation. In this comparison, the differential effect of arterialized collateral blood flow compared to retrograde venous blood flow low in oxygen has to be taken into account. In other words, the same rate of arterial coronary blood flow is more effective in reducing myocardial ischemia, than venous blood retroperfusate, where oxygen extraction is conceivably much lower.

Regarding the well-documented effect of antegrade flow inhibition, the model predicted the same for collateral blood flow, which was more reduced at higher collateral

flows and showed a curvilinear relation with ECP. To summarize, the findings of the computer model are in agreement with the clinical study. The prediction of low retrograde flow at low collateral function is consistent with the observed absence of an ischemia-reducing effect with CSO. With sufficient collateral function, the model predicted an increase in retrograde flow, which did however not translate in a further reduction in ischemia in the clinical study, given that it was abolished by collaterals in the first place. Retrograde flow had an ischemia-reducing effect at intermediate, but insufficient levels of collateral function. Given these points, the bell-shaped relation between ischemia reduction and collateral function seen in the clinical study is compatible with the mathematical model.

Role of coronary collaterals: implications for clinical application

Intermittent coronary sinus occlusion (ICSO) has recently been reinvestigated as an adjunct to PCI in patients with acute myocardial ischemia. A preliminary, uncontrolled safety and feasibility study included 19 patients undergoing PCI of a LAD culprit lesion with anterior ST-segment elevation myocardial infarction (STEMI). In patients successfully treated with (pressure-controlled) ICSO, there was greater infarct size reduction compared with matched historic controls.[121] Of note, the study excluded patients with cardiogenic shock. By the same token, an interim analysis of an ongoing controlled, but not randomized trial in patients with acute coronary syndrome showed a significant reduction in infarct size of 10.6% points in patients undergoing ICSO relative to patients not undergoing the intervention. Furthermore, a reduction in microvascular obstruction was observed.[122]

In the context of the findings from our clinical study and the prediction by the mathematical model, it might be worthwhile to additionally evaluate the influence of collateral status on the effectiveness of ICSO in this setting. As a first approximation, an evaluation by the angiographic Rentrop score would provide a simple approach to gauge collateral function, given its ready availability during coronary angiography.

Similarly, but in the setting of chronic ischemia, the clinical use of a coronary sinus reducer stent, can be likened to a form of incomplete CSO, leading to chronic as opposed to intermittent elevation of CSP. A preliminary safety feasibility study [50] and the following randomized, sham-controlled clinical study[52] showed symptomatic

improvement in a majority, but not all patients undergoing the device implantation for refractory angina. The mechanism of "recruitment of collateral flow" purported by the authors is however inconsistent with the notion of increased CSP leading to a flow diversion from non-ischemic to ischemic zones augmented by collateral function indirectly. Clinically, this notion might have implications for patient selection both in the acute and chronic setting of myocardial ischemia. In other words, patients with minimal collateral function might conceivably derive less benefit from CSI compared to patients with higher levels of collateral function. In the setting of acute myocardial ischemia this consideration in particular applies to patients with cardiogenic shock, where poor collateral function is more common.[123, 124] In patients with chronic myocardial ischemia, such as in the setting of CTO, collateral function is typically much higher[125] and the effect of CSP elevation might therefore be more beneficial.

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Appendices

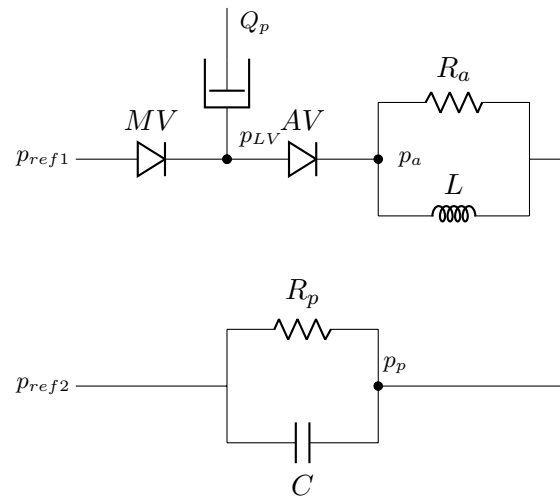


Figure 1: Lumped parameter model: Model input

Code

Listing 1: Matlab code for the main function of the model

```
1 clearvars except argnum doplot iteratemode; close all; clc
2
3 if nargin < 1
4     argnum = 1;
5     doplot = 0;
6 elseif nargin < 2
7     doplot = 0;
8 end
9
10 %% get parameters from separate excel file
11
12 warning off
13     param_tbl = readtable(fullfile(pwd, 'param_double2c_minimi_5.xlsx
        '));
14 warning on
15
16 % set param names and values
17
18 tbl_length = find(cellfun(@(x) isempty(x), param_tbl{:,1}), 1); %
        exclude empty rows
19
20 if isempty(tbl_length)
21     tbl_length = length(param_tbl{:,1});
22 end
23
24 for i = 1:tbl_length
25     for k = 1:(width(param_tbl) - 1)
26         Arglist{k}.(char(param_tbl{i,1})) = param_tbl{i,k+1};
27     end
```

```

28 end
29
30 %% check parameters
31
32 if nargin < 1
33     Arg = Arglist{1};
34 else
35     Arg = Arglist{argnum};
36 end
37
38 %% get input: LVP and pao
39
40 [time, LVP, pao, BPM] = linear_drive_load_setup_2(0, Arg.beats_n); %
    generate pulses, n=Arg.beats_n
41
42 % period
43 period = 60/BPM; % [s]
44
45 % LVP dot, ECP dot
46 [dLVPdt] = central_diff(LVP, time);
47
48 % ECP = LVP*lvpscale;
49
50 ECP_L1 = LVP*Arg.lvpscale*Arg.gamma_L1;
51 ECP_L2 = LVP*Arg.lvpscale*Arg.gamma_L2;
52
53 [dECPdt_L1] = central_diff(ECP_L1, time);
54 [dECPdt_L2] = central_diff(ECP_L2, time);
55
56 input = {time, pao, LVP, ECP_L1, ECP_L2, BPM};
57
58 % right atrial pressure
59
60 pRA = repmat(700, length(pao), 1);
61 pex1 = LVP;
62 pex2 = pRA;
63
64 %% initial state
65
66 % initial conditions

```

```

67 p_0 = [ Arg.p0_aepi1 , Arg.p0_ai1 , Arg.p0_cap1 , Arg.p0_aepi2 , Arg.
        p0_ai2 , Arg.p0_cap2 , Arg.p0_ven , ...
68         Arg.V0_aepi_L1*1e 6 , Arg.V0_ai_L1*1e 6 , Arg.V0_cap_L1*1e 6 , Arg.
        V0_aepi_L2*1e 6 , Arg.V0_ai_L2*1e 6 , Arg.V0_cap_L2*1e 6 , Arg.
        V0_vepi*1e 6 ];

69
70 t_span = [time(1) , time(end)];
71
72 %% solver , ode15s
73
74 options = odeset( 'Mass',@(t, p) mass(t, p, Arg, time, ECP_L1, ECP_L2,
        pex1, pex2), 'RelTol',Arg.RelTol); % set options for solver
75
76 %% node names
77
78 p_nodes = {
79     'L1aepi'
80     'L1ai'
81     'L1cap'
82     'L2aepi'
83     'L2ai'
84     'L2cap'
85     'Lvepi'
86 };
87
88 q_labels = {
89     'RL1aepi'; % 1
90     'RL1ai'; % 2
91     'RL1cap'; % 3
92     'RL2aepi'; % 4
93     'RL2ai'; % 5
94     'RL2cap'; % 6
95     'RL1vepi'; % 7
96     'RL2vepi'; % 8
97     'RL1ex'; % 9
98     'RL2ex'; %10
99     'Rcai'; %11
100    'Rcven'; %12
101    'Rex2'; %13
102    'RCS'; %14
103 };

```

```

104
105 r_labels = {
106     'RL1aepi'; % 1
107     'RL1ai'; % 2
108     'RL1cap'; % 3
109     'RL2aepi'; % 4
110     'RL2ai'; % 5
111     'RL2cap'; % 6
112     'RL1vepi'; % 7
113     'RL2vepi'; % 8
114     'RL1ex'; % 9
115     'RL2ex'; %10
116     'Rcai'; %11
117     'Rcven'; %12
118     'Rex2'; %13
119     'RCS'; %14
120 };
121
122 v_labels = {
123     'L1aepi' % 1
124     'L1ai' % 2
125     'L1cap' % 3
126     'L2aepi' % 4
127     'L2ai' % 5
128     'L2cap' % 6
129     'Lven' % 7
130 };
131
132 %% solve system for pressures and volumes
133
134 [T, P] = ode15s(@(t, p) rhs(t, p, Arg, time, LVP, ECP_L1, ECP_L2,
    dECPdt_L1, dECPdt_L2, pao, pRA, pex1, pex2), t_span, p_0, options);
135
136 %% calculate flows in nodes
137
138 [T, Q, V, r, c, c_ratio] = flows(T, P, pao, Arg, LVP, dECPdt_L1,
    dECPdt_L2, time, ECP_L1, ECP_L2, pex1, pex2);
139
140 %% plotting
141
142 if doplot == 1

```



```

143
144     xlim_fig(1) = 1; % [sec]
145     xlim_fig(2) = T(end);
146
147     lw = 1.5; % linewidth
148     fs_label = 18; % font size for axis labels
149
150
151     %% figure 1: pressures coronary L1
152
153     hf1 = figure();
154
155     xlim(xlim_fig)
156
157     hold on; grid on;
158
159     title1 = title([param_tbl(:,argnum+1).Properties.VariableNames,'_L1'
160                    ]);
161
162     for k = [1:3,7]
163         if k == 3 % plot aortic, right atrial and LV pressure
164             plot(time,pRA/133.3,'c','linewidth',lw,'DisplayName','P_RA
165                  '); hold on;
166             plot(time,pao/133.3,'c','linewidth',lw,'DisplayName','P_ao
167                  '); hold on;
168             % plot(time,LVP/133.3,'r','linewidth',lw,'DisplayName','
169                  LVP'); hold on;
170         end
171
172         if k == 1
173             plot(T, P(:,k)/133.3,'.', 'linewidth',lw,'DisplayName',[ '
174                  P_',p_nodes{k}]); hold on;
175         elseif k == 2
176             plot(T, P(:,k)/133.3,' ', 'linewidth',lw,'DisplayName',[ '
177                  P_',p_nodes{k}]); hold on;
178         elseif k == 3
179             plot(T, P(:,k)/133.3,':', 'linewidth',lw,'DisplayName',[ 'P_
180                  ',p_nodes{k}]); hold on;
181         else
182             plot(T, P(:,k)/133.3,':', 'linewidth',lw,'DisplayName',[ 'P_
183                  ',p_nodes{k}]); hold on;

```

```

176         end
177
178     end
179
180     xlabel('time_t[s]', 'FontSize', fs_label)
181     ylabel('pressure_mmHg', 'FontSize', fs_label)
182
183     xlim(xlim_fig)
184     set(gca, 'FontSize', 16)
185
186     leg1 = legend('DynamicLegend');
187     set(leg1, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
188     set(title1, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
189
190     %% figure 2: pressures coronary L2
191
192     hf2 = figure();
193
194     xlim(xlim_fig)
195
196     hold on; grid on;
197
198     title2 = title([param_tbl(:, argnum+1).Properties.VariableNames, 'L2'
        ]);
199
200     for k = 4:7
201         if k == 4 % plot aortic pressure
202             plot(time, pRA/133.3, 'c', 'linewidth', lw, 'DisplayName', 'P_RA
                '); hold on;
203             plot(time, pao/133.3, 'c', 'linewidth', lw, 'DisplayName', 'P_ao
                '); hold on;
204 %             plot(time, LVP/133.3, 'r', 'linewidth', lw, 'DisplayName', '
                LVP'); hold on;
205         end
206         plot(T, P(:, k)/133.3, 'linewidth', lw, 'DisplayName', ['P_',
            p_nodes{k}]); hold on;
207     end
208
209     xlabel('time_t[s]', 'FontSize', fs_label)

```

```

210     ylabel('pressure_ [mmHg] ', 'FontSize', fs_label)
211
212     xlim(xlim_fig)
213     set(gca, 'FontSize', 16)
214
215     leg2 = legend(' DynamicLegend');
216     set(leg2, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
217     set(title2, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
218
219     %% figure 3: flows
220
221     hf3 = figure();
222     xlim(xlim_fig)
223
224     hold on; grid on;
225
226     lw = 1.2;
227
228     title3 = title(param_tbl(:, argnum+1).Properties.VariableNames);
229     set(title3, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
230
231     %%
232     sp(1) = subplot(6, 1, 1:2);
233
234     xlim(xlim_fig)
235     set(gca, 'FontSize', 16)
236     hold on; grid on;
237
238     for k = [1:3]
239         plot(T, Q(:, k)*1e6/100*60, 'linewidth', lw, 'DisplayName', ['I_',
            q_labels{k}]); hold on;
240     end
241
242     ylabel('Arterial_Flow_ [ml/min] _per_g')
243     leg3_1 = legend(' DynamicLegend');
244     set(leg3_1, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
245

```

```

246 %%
247 sp(2) = subplot (6,1,3:4);
248
249 xlim(xlim_fig)
250 set(gca,'FontSize',16)
251 hold on; grid on;
252
253 for k = [11:12]
254     plot(T, Q(:,k)*1e6/100*60, 'linewidth', lw, 'DisplayName', ['I_',
        q_labels{k}]); hold on;
255 end
256
257 ylabel('Collateral_Flow_[ml/min]_per_g')
258 leg3_1 = legend('DynamicLegend');
259 set(leg3_1, 'Interpreter', 'none'); % turn off Interpreter to avoid
    subscript when using '_'
260
261 %%
262 sp(3) = subplot (6,1,5:6);
263
264 xlim(xlim_fig)
265 set(gca,'FontSize',16)
266 hold on; grid on;
267
268 % for k = [7:13]
269 for k = [7,9,11:14]
270     if k == 12
271         plot(T, Q(:,k)*1e6/200*60, 'linewidth', lw, 'DisplayName', ['
            I_', q_labels{k}]); hold on;
272     else
273         plot(T, Q(:,k)*1e6/100*60, 'linewidth', lw, 'DisplayName', ['
            I_', q_labels{k}]); hold on;
274     end
275 end
276
277 xlabel('time_t_[s]', 'FontSize', fs_label)
278 ylabel('Venous_Flow_[ml/min]_per_g', 'FontSize', fs_label)
279 set(gca,'FontSize',16)
280
281 linkaxes(sp, 'x')
282

```

```

283     leg3_2 = legend(' DynamicLegend');
284     set(leg3_2, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '-'
285
286     %% figure 3: volumes
287
288     hf3 = figure();
289
290     hold on; grid on;
291
292     lw = 1.5;
293
294     title3 = title(param_tbl(:,argnum+1).Properties.VariableNames);
295
296     for k = [1:7]
297         plot(T, V(:,k), 'linewidth', lw, 'DisplayName', ['V-', v_labels{k}
            ]); hold on;
298     end
299
300     xlabel('time_t[s]', 'FontSize', fs_label)
301     ylabel('Volume[ml]', 'FontSize', fs_label)
302
303     xlim(xlim_fig);
304     set(gca, 'FontSize', 16)
305
306     leg3 = legend(' DynamicLegend');
307     set(leg3, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '-'
308     set(title3, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '-'
309
310     %% figure 4: resistances
311
312     hf4 = figure();
313
314     hold on; grid on;
315
316     lw = 1.5;
317
318     title4 = title(param_tbl(:,argnum+1).Properties.VariableNames);
319

```

```

320     for k = [2:13]
321         plot(T, r(:,k), 'linewidth', lw, 'DisplayName', ['r_', r_labels{k}
322             ]]); hold on;
323     end
324     set(gca, 'FontSize', 16)
325
326     xlabel('time_t[s]', 'FontSize', fs_label)
327     ylabel('resistance_[Pa_s/m^3]', 'FontSize', fs_label)
328
329     xlim(xlim_fig)
330
331     leg4 = legend('DynamicLegend');
332     set(leg4, 'Interpreter', 'none'); % turn off Interpreter to avoid
333         subscript when using '-'
334
335     set(title4, 'Interpreter', 'none'); % turn off Interpreter to avoid
336         subscript when using '-'
337
338     %% figure 5: compliances
339
340     hf5 = figure();
341
342     hold on; grid on;
343
344     lw = 1.5;
345
346     title5 = title(param_tbl(:, argnum+1).Properties.VariableNames);
347
348     for k = [1:7]
349         plot(T, c(:,k), 'linewidth', lw, 'DisplayName', ['c_', v_labels{k}
350             ]]); hold on;
351     end
352
353     xlabel('time_t[s]', 'FontSize', fs_label)
354     ylabel('compliance_[m^3_/Pa]', 'FontSize', fs_label)
355
356     xlim(xlim_fig)
357     set(gca, 'FontSize', 16)
358
359     leg5 = legend('DynamicLegend');

```

```

356     set(leg5, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
357     set(title5, 'Interpreter', 'none'); % turn off Interpreter to avoid
        subscript when using '_'
358
359
360 end
361
362 disp('*****')
363 disp('done')
364 disp('*****')
365
366 end
367
368 %

369
370 %% function for input of right hand side (ode15s)
371
372 function [M_dpdtd] = rhs(t, p, Arg, time, LVP, ECP_L1, ECP_L2, dECPdt_L1,
        dECPdt_L2, pao, pRA, pex1, pex2)
373
374 % interpolate input data
375
376 pa = interp1(time, pao, t);
377 lvp = interp1(time, LVP, t);
378
379 ecp_l1 = interp1(time, ECP_L1, t);
380 ecp_l2 = interp1(time, ECP_L2, t);
381
382 ecpdot_l1 = interp1(time, dECPdt_L1, t);
383 ecpdot_l2 = interp1(time, dECPdt_L2, t);
384
385 pra = 700;
386
387 pex1 = interp1(time, pex1, t, 'pchip');
388 pex2 = interp1(time, pex2, t, 'pchip');
389
390 % calculate variable resistances
391

```

```

392 [r, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, v, v1,
    v2, v3, v4, v5, v6, v7] = resistances(t, p, ecp_l1, ecp_l2, Arg, 0,
    pex1, pex2);
393
394 % calculate variable compliances
395
396 [~, C1, C2, C3, C4, C5, C6, C7, ~] = compliances(t, p, ecp_l1, ecp_l2,
    Arg, 0, v3, v6, v7, v);
397
398 % capillary pressures
399
400 if Arg.pforced
401     p(3) = ( p(10)/ C3 ) + ecp_l1;
402     p(6) = ( p(13)/ C6 ) + ecp_l2;
403 end
404
405 % venous pressure
406
407 if Arg.pforced
408     p(7) = (v7 * Arg.chi_ven ^ 2 * exp(Arg.sigma_ven*(v7 - Arg.V0_vepi))
    ) * 133.3;
409 end
410
411 % pressure for venous collaterals
412
413 p3_cven = Arg.p_cven_factor * p(3) + 1333;
414 p6_cven = Arg.p_cven_factor * p(6) + 1333;
415
416 % define right hand side
417 M_dpdt = zeros(14,1); % initialize
418
419 M_dpdt(1) = 1/R1* (pa - p(1)) - 1/R2* (p(1) - p(2));
    % node 1
420 M_dpdt(2) = 1/R2* (p(1) - p(2)) - 1/R3* (p(2) - p(3)) - 1/R11*(p(2) - p
    (5)) + C2*ecp_dot_l1;
    % node 2
421
422 if Arg.cven
423     M_dpdt(3) = 1/R3* (p(2) - p(3)) - 1/R7*(p(3) - p(7)) - 1/R9*(p(3)
    pex1 + Arg.p_off_cap) - 1/R12*(p3_cven - p(6)) + C3*ecp_dot_l1;

```



```

                                % node 3 with collateral
424 else
425     M_dpdt(3) = 1/R3* (p(2)    p(3))    1/R7*(p(3)    p(7))    1/R9*(p(3)
        pex1 + Arg.p_off_cap) + C3*ecpdot_l1;
                                % node 3
426 end
427
428 M_dpdt(4) = 1/R4* (pa    p(4))    1/R5* (p(4)    p(5));

                                % node 4
429 M_dpdt(5) = 1/R5* (p(4)    p(5))    1/R6* (p(5)    p(6)) + 1/R11*(p(2)    p
        (5)) + C5*ecpdot_l2;
                                % node 5
430
431 if Arg.cven
432     M_dpdt(6) = 1/R6* (p(5)    p(6))    1/R8*(p(6)    p(7))    1/R10*(p(6)
        pex1 + Arg.p_off_cap) + 1/R12*(p3_cven    p(6)) + C6*ecpdot_l2;
                                % node 6 with collateral
433 else
434     M_dpdt(6) = 1/R6* (p(5)    p(6))    1/R8*(p(6)    p(7))    1/R10*(p(6)
        pex1 + Arg.p_off_cap) + C6*ecpdot_l2;
                                % node 6
435 end
436
437 M_dpdt(7) = 1/R7* (p(3)    p(7)) + 1/R8*(p(6)    p(7))    1/R13*(p(7)
        pex2 + Arg.p_off_ven)    1/R14*(p(7)    pra);
                                % node 7
438 M_dpdt(8) = 0;

                                % volume in C1
439 M_dpdt(9) = C2*ecpdot_l1;

                                % volume in C2
440 M_dpdt(10) = C3*ecpdot_l1;

                                % volume in C3
441 M_dpdt(11) = 0;

                                % volume in C4
442 M_dpdt(12) = C5*ecpdot_l2;

```

```

        % volume in C5
443 M_dpdt(13) = C6*ecpdot_l2;

        % volume in C6
444 M_dpdt(14) = 0;

        % volume in C7
445
446 end
447
448 %

449
450 %% function for input of mass matrix (ode15s)
451
452 function [M] = mass(t, p, Arg, time, ECP_L1, ECP_L2, pex1, pex2)
453
454 ecp_l1 = interp1(time, ECP_L1, t, 'pchip');
455 ecp_l2 = interp1(time, ECP_L2, t, 'pchip');
456
457 [r, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, v, v1,
    v2, v3, v4, v5, v6, v7] = resistances(t, p, ecp_l1, ecp_l2, Arg, 0,
    pex1, pex2);
458
459 [c, C1, C2, C3, C4, C5, C6, C7, c_ratio] = compliances(t, p, ecp_l1,
    ecp_l2, Arg, 0, v3, v6, v7, v);
460
461 % mass matrix
462
463      %1      %2      %3      %4      %5      %6      %7      %8      %9      %10      %11      %12      %13
      %14
464 M = [C1,      0,      0,      0,      0,      0,      0,      0,      0,      0,      0,      0,      0,
      0;          % node 1
465      0,      C2,      0,      0,      0,      0,      0,      0,      0,      0,      0,      0,      0,
      0;          % node 2
466      0,      0,      C3,      0,      0,      0,      0,      0,      0,      0,      0,      0,      0,
      0;          % node 3
467      0,      0,      0,      C4,      0,      0,      0,      0,      0,      0,      0,      0,      0,
      0;          % node 4

```

```

468      0,      0,      0,      0, C5,      0,      0,      0,      0,      0,      0,      0,      0,
         0;          % node 5
469      0,      0,      0,      0,      0, C6,      0,      0,      0,      0,      0,      0,      0,
         0;          % node 6
470      0,      0,      0,      0,      0,      0, C7,      0,      0,      0,      0,      0,      0,
         0;          % node 7
471      C1,      0,      0,      0,      0,      0,      0,      1,      0,      0,      0,      0,      0,
         0;          % volume in C1
472      0,      C2,      0,      0,      0,      0,      0,      0,      1,      0,      0,      0,      0,
         0;          % volume in C2
473      0,      0,      C3,      0,      0,      0,      0,      0,      0,      1,      0,      0,      0,
         0;          % volume in C3
474      0,      0,      0,      C4,      0,      0,      0,      0,      0,      0,      1,      0,      0,
         0;          % volume in C4
475      0,      0,      0,      0,      C5,      0,      0,      0,      0,      0,      0,      1,      0,
         0;          % volume in C5
476      0,      0,      0,      0,      0,      C6,      0,      0,      0,      0,      0,      0,      1,
         0;          % volume in C6
477      0,      0,      0,      0,      0,      0,      C7,      0,      0,      0,      0,      0,      0,
         1];          % volume in C7
478
479  end
480
481  % subfunction for instantaneous resistances
482
483  function [r, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14
         , v, v1, v2, v3, v4, v5, v6, v7] = resistances(t, p, ecp_l1, ecp_l2,
         Arg, arrayfun, pex1, pex2)
484
485  % resistances
486
487  R1_0 = Arg.RL1aepi;
488  R2_0 = Arg.RL1ai;
489  R3_0 = Arg.RL1cap;
490
491  R4_0 = Arg.RL2aepi;
492  R5_0 = Arg.RL2ai;
493  R6_0 = Arg.RL2cap;
494
495  R7_0 = Arg.RL1vepi;
496  R8_0 = Arg.RL2vepi;

```

```

497 R9_0 = Arg.RL1ex;
498 R10_0 = Arg.RL2ex;
499
500 R11_0 = Arg.Rcai;
501 R12_0 = Arg.Rcven;
502 R13_0 = Arg.RLex;
503
504 r_factor = Arg.r_factor;
505
506 %           unpack arguments end
507
508 if ~arrayfun
509
510     % first coronary
511
512     v1 = p(8)*1e6; % volume in C1, from [m3] to [ml]
513     v2 = p(9)*1e6; % volume in C2, from [m3] to [ml]
514     v3 = p(10)*1e6; % volume in C3, from [m3] to [ml]
515
516     % second coronary
517
518     v4 = p(11)*1e6; % volume in C4, from [m3] to [ml]
519     v5 = p(12)*1e6; % volume in C5, from [m3] to [ml]
520     v6 = p(13)*1e6; % volume in C6, from [m3] to [ml]
521
522     % epicardial vein
523
524     v7 = p(14)*1e6; % volume in C7, from [m3] to [ml]
525
526     % resistances
527
528     R1 = R1_0;
529     R2 = R2_0;
530
531     % prevent emptying of compartments
532
533     if p(2) p(3) > 0
534         R3 = R3_0 + ( r_factor * p(9) ) ^ 2; % p(9) is volume in C2
535     else
536         R3 = R3_0 + ( r_factor * p(10) ) ^ 2; % p(10) is volume in C3
537     end

```

```

538
539 R4 = R4_0;
540 R5 = R5_0;
541
542 if p(5) p(6) > 0
543     R6 = R6_0 + ( r_factor * p(12)) ^ 2; % p(12) is volume in C5
544 else
545     R6 = R6_0 + ( r_factor * p(13)) ^ 2; % p(13) is volume in C6
546 end
547
548 if p(3) p(7) > 0
549     R7 = R7_0 + ( r_factor * p(10)) ^ 2; % p(10) is volume in C3
550 else
551     R7 = R7_0 + ( r_factor * p(14)) ^ 2; % p(14) is volume in C7
552 end
553
554 if p(6) p(7) > 0
555     R8 = R8_0 + ( r_factor * p(13)) ^ 2; % p(13) is volume in C6
556 else
557     R8 = R8_0 + ( r_factor * p(14)) ^ 2; % p(14) is volume in C7
558 end
559
560 % extra outlet L1 (thebesian)
561
562 if p(3) pex1 > 0
563     R9 = R9_0 + ( r_factor * p(10)) ^ 2;
564 else
565     R9 = R9_0;
566 end
567
568 % extra outlet L2 (thebesian)
569
570 if p(6) pex1 > 0
571     R10 = R10_0 + ( r_factor * p(13)) ^ 2; % p(13) is volume in C6
572 else
573     R10 = R10_0;
574 end
575
576 R11 = R11_0;
577
578 % venous collateral

```

```

579
580     if p(6) p(3) > 0
581         R12 = R12_0 + ( r_factor * p(13)) ^ 2; % p(13) is volume in C6
582     else
583         R12 = R12_0+ ( r_factor * p(10)) ^ 2; % p(10) is volume in C3
584     end
585
586     % extra outlet
587
588     if p(7) pex2 > 0
589         R13 = R13_0 + ( r_factor * p(14)) ^ 2; % p(14) is volume in C7 ;
590     else
591         R13 = R13_0;
592     end
593
594     % intermittent CS occlusion
595
596     if t < 15 % reach steady state
597         R14 = Arg.RCS_nonoccl;
598     elseif t < 25
599         R14 = Arg.RCS_occl;
600     elseif t < 30
601         R14 = Arg.RCS_nonoccl;
602     elseif t < 40
603         R14 = Arg.RCS_occl;
604     elseif t < 45
605         R14 = Arg.RCS_nonoccl;
606     elseif t < 55
607         R14 = Arg.RCS_occl;
608     elseif t <= 60
609         R14 = Arg.RCS_nonoccl;
610     end
611
612     r = [];
613     v = [];
614     v_ratio = [];
615
616 else
617     for k = 1 : length(t)
618
619         %% volumes

```

```

620
621 % first coronary
622
623 v(k,1) = p(k,8)*1e6; % volume in C1, from [m3] to [ml]
624 v(k,2) = p(k,9)*1e6;
625 v(k,3) = p(k,10)*1e6;
626
627 % second coronary
628
629 v(k,4) = p(k,11)*1e6; % volume in C3, from [m3] to [ml]
630 v(k,5) = p(k,12)*1e6;
631 v(k,6) = p(k,13)*1e6;
632
633 % epicardial vein
634
635 v(k,7) = p(k,14)*1e6;
636
637 %% resistances
638
639 % first coronary
640
641 r(k,1) = R1_0;
642 r(k,2) = R2_0;
643
644 % prevent emptying of C2, arterial intramyocardial compartment
645
646 if p(k,2) p(k,3) > 0
647     r(k,3) = R3_0 + ( r_factor * p(k,9)) ^ 2;
648 else
649     r(k,3) = R3_0 + ( r_factor * p(k,10)) ^ 2;
650 end
651
652 % prevent emptying of C3, capillary compartment
653
654 if p(k,3) p(k,7) > 0
655     r(k,7) = R7_0 + ( r_factor * p(k,10)) ^ 2;
656 else
657     r(k,7) = R7_0 + ( r_factor * p(k,14)) ^ 2;
658 end
659
660 % second coronary

```

```

661
662     r(k,4) = R4_0;
663     r(k,5) = R5_0;
664
665     % prevent emptying of C5, arterial intramyocardial compartment
666
667     if p(k,5) p(k,6) > 0
668         r(k,6) = R6_0 + ( r_factor * p(k,12)) ^ 2;
669     else
670         r(k,6) = R6_0 + ( r_factor * p(k,13)) ^ 2;
671     end
672
673     % prevent emptying of C6, capillary compartment
674
675     if p(k,6) p(k,7) > 0
676         r(k,8) = R8_0 + ( r_factor * p(k,13)) ^ 2;
677     else
678         r(k,8) = R8_0 + ( r_factor * p(k,14)) ^ 2;
679     end
680
681     % extra outlet L1 (thebesian)
682
683     if p(k,3) pex1(k) > 0
684         r(k,9) = R9_0 + ( r_factor * p(k,10)) ^ 2;
685     else
686         r(k,9) = R9_0;
687     end
688
689     % extra outlet L2 (thebesian)
690
691     if p(6) pex1(k) > 0
692         r(k,10) = R10_0 + ( r_factor * p(k,13)) ^ 2; % p(13) is volume in
        C6
693     else
694         r(k,10) = R10_0;
695     end
696
697     r(k,11) = R11_0;
698
699     % venous collateral
700

```



```

701     if p(6) p(3) > 0
702         r(k,12) = R12_0 + ( r_factor * p(13)) ^ 2; % p(13) is volume in
              C6
703     else
704         r(k,12) = R12_0 + ( r_factor * p(10)) ^ 2; % p(10) is volume in
              C3
705     end
706
707     % coronary sinus
708
709     % prevent emptying of C7, venous compartment
710
711     if p(k,7) pex2(k) > 0
712         r(k,13) = R13_0 + ( r_factor * p(k,14)) ^ 2;
713     else
714         r(k,13) = R13_0;
715     end
716
717     % intermittent CS occlusion
718
719     if t(k) < 15 % reach steady state
720         r(k,14) = Arg.RCS_nonoccl;
721     elseif t(k) < 25
722         r(k,14) = Arg.RCS_occl;
723     elseif t(k) < 30
724         r(k,14) = Arg.RCS_nonoccl;
725     elseif t(k) < 40
726         r(k,14) = Arg.RCS_occl;
727     elseif t(k) < 45
728         r(k,14) = Arg.RCS_nonoccl;
729     elseif t(k) < 55
730         r(k,14) = Arg.RCS_occl;
731     elseif t(k) <= 60
732         r(k,14) = Arg.RCS_nonoccl;
733     end
734
735     end
736
737     R1 = [];
738     R2 = [];
739     R3 = [];

```

```

740     R4 = [];
741     R5 = [];
742     R6 = [];
743     R7 = [];
744     R8 = [];
745     R9 = [];
746     R10 = [];
747     R11 = [];
748     R12 = [];
749     R13 = [];
750     R14 = [];
751
752     v1 = [];
753     v2 = [];
754     v3 = [];
755     v4 = [];
756     v5 = [];
757     v6 = [];
758     v7 = [];
759
760 end
761
762 end
763
764 % subfunction for instantaneous compliances
765
766 function [c, C1, C2, C3, C4, C5, C6, C7, c_ratio] = compliances(t, p,
    ecp_l1, ecp_l2, Arg, arrayfun, v3, v6, v7, v)
767
768 %         unpack arguments start
769
770 % compliances
771
772 C1_0 = Arg.CL1aepi;
773 C2_0 = Arg.CL1ai;
774 C3_0 = Arg.CL1cap;
775
776 C4_0 = Arg.CL2aepi;
777 C5_0 = Arg.CL2ai;
778 C6_0 = Arg.CL2cap;
779

```

```

780 C7_0 = Arg.CLvepi;
781
782 % reference volumes
783
784 V0_vepi = Arg.V0_vepi;
785 sigma_ven = Arg.sigma_ven;
786
787 %           unpack arguments end
788
789 if ~arrayfun
790
791     C1 = C1_0;
792     C2 = C2_0;
793
794     if Arg.C_cap_var == 0
795         C3 = C3_0;
796     else
797         C3 = C3_0 * (1 + Arg.sigma_cap * v3).^ 1 * exp( Arg.sigma_cap*(
              v3    Arg.V0_cap_L1)); % volumes in [ml]
798     end
799
800     C4 = C4_0;
801     C5 = C5_0;
802
803     if Arg.C_cap_var == 0
804         C6 = C6_0;
805     else
806         C6 = C6_0 * (1 + Arg.sigma_cap * v6).^ 1 * exp( Arg.sigma_cap*(
              v6    Arg.V0_cap_L2));
807     end
808
809     C7 = C7_0 * (1 + sigma_ven * v7).^ 1 * exp( sigma_ven*(v7    V0_vepi)
              );
810
811     c = [];
812     c_ratio = [];
813
814 else
815     for k = 1 : size(t,1)
816
817         % first coronary

```

```

818
819     c_ratio(k,1) = 1;
820     c_ratio(k,2) = 1;
821
822     if Arg.C_cap_var == 0
823         c_ratio(k,3) = 1;
824     else
825         c_ratio(k,3) = (1 + Arg.sigma_cap * v(k,3))^1 .* exp( Arg.
            sigma_cap * (v(k,3) - Arg.V0_cap_L1)); % volumes in [ml
            ];
826     end
827
828     % second coronary
829
830     c_ratio(k,4) = 1;
831     c_ratio(k,5) = 1;
832
833     if Arg.C_cap_var == 0
834         c_ratio(k,6) = 1;
835     else
836         c_ratio(k,6) = (1 + Arg.sigma_cap * v(k,6))^1 .* exp( Arg.
            sigma_cap * (v(k,6) - Arg.V0_cap_L2)); % volumes in [ml
            ];
837     end
838
839     % compliance for venous segment is volume dependent
840
841     c_ratio(k,7) = (1 + sigma_ven * v(k,7))^1 .* exp( sigma_ven * (
            v(k,7) - V0_vepi)); % volumes in [ml]
842     end
843
844     c(:,1) = C1_0 .* c_ratio(:,1);
845     c(:,2) = C2_0 .* c_ratio(:,2);
846     c(:,3) = C3_0 .* c_ratio(:,3);
847     c(:,4) = C4_0 .* c_ratio(:,4);
848     c(:,5) = C5_0 .* c_ratio(:,5);
849     c(:,6) = C6_0 .* c_ratio(:,6);
850     c(:,7) = C7_0 .* c_ratio(:,7);
851
852     C1 = [];
853     C2 = [];

```

```

854     C3 = [];
855     C4 = [];
856     C5 = [];
857     C6 = [];
858     C7 = [];
859 end
860
861 end
862
863 % function for output of node flows and volumes
864
865 function [T, Q, v, r, c, c_ratio] = flows(T, P, PAO, Arg, LVP, dECPdt.L1
    , dECPdt.L2, time, ecp_l1, ecp_l2, pex1, pex2)
866
867 % interpolate inputs
868 pao = interp1(time, PAO, T, 'pchip');
869 lvp = interp1(time, LVP, T, 'pchip');
870 pex1 = interp1(time, pex1, T, 'pchip');
871 pex2 = interp1(time, pex2, T, 'pchip');
872 pra = 700;
873
874 decpdt_l1 = interp1(time, dECPdt.L1, T, 'pchip');
875 decpdt_l2 = interp1(time, dECPdt.L2, T, 'pchip');
876
877 % get variable resistances
878 [r, ~, ~, ~, ~, ~, ~, ~, ~, ~, ~, ~, ~, ~, v, v1, v2, v3, v4, v5, v6
    , v7] = resistances(T, P, ecp_l1, ecp_l2, Arg, 1, pex1, pex2);
879
880 % get variable compliances
881 [c, ~, ~, ~, ~, ~, ~, c_ratio] = compliances(T, P, ecp_l1, ecp_l2, Arg,
    1, v3, v6, v7, v);
882
883 %% flows
884
885 Q(:,1) = (pao - P(:,1))./r(:,1);
886 Q(:,2) = (P(:,1) - P(:,2))./r(:,2);
887 Q(:,3) = (P(:,2) - P(:,3))./r(:,3);
888
889 Q(:,4) = (pao - P(:,4))./r(:,4);
890 Q(:,5) = (P(:,4) - P(:,5))./r(:,5);
891 Q(:,6) = (P(:,5) - P(:,6))./r(:,6);

```

```

892
893 Q(:,7) = (P(:,3) - P(:,7))./r(:,7);
894 Q(:,8) = (P(:,6) - P(:,7))./r(:,8);
895
896 Q(:,9) = (P(:,3) - pex1 + Arg.p_off_cap)./r(:,9);
897 Q(:,10) = (P(:,6) - pex1 + Arg.p_off_cap)./r(:,10);
898
899 Q(:,11) = (P(:,2) - P(:,5))./r(:,11);
900
901 if Arg.cven
902     disp('calculating_venous_collateral_flow')
903     Q(:,12) = ((P(:,3)*Arg.p_cven_factor +1333 - Arg.p_off_cven) - (P
        (:,6)*Arg.p_cven_factor+1333 - Arg.p_off_cven))./r(:,12);
904 end
905 % Q(:,12) = []
906
907 Q(:,13) = (P(:,7) - pex2 )./r(:,13); % Arg.p_off_ven
908 Q(:,14) = (P(:,7) - pra)./r(:,14);
909
910 end

```

Listing 2: Matlab code for the input to the main function

```

1 function [T, LVP, pao, BPM] = linear_drive_load_setup_2(showplot, N_puls)
2 %

3 % This is a MATLAB m file
4 %

5 % File : linear_drive_load_setup_2.m
6 % Author : David Hasler, Michael Stoller (some modifications)
7 % Date : 2016 06 21
8 % Last Change : 2017 01 14
9 % Institute : ARTORG and Cardiology, Bern University Hospital, Bern,
10 % Switzerland
11 % Topic : Load on linear drive, LPM systemic circulation, tomo
    piv setup 2.0
12 %

13 % Description:
14 % The load on the linear drive screw used in the pump of the flow loop
    can
15 % be determined by the linear momentum equation (Impulssatz). To
    determine
16 % the load from the pressure on the cylinder surface a lumped parameter
17 % lumped paR-ometer model (LPM) is applied. To this puR-ose, the LPM
18 % 'flowloop-setup-2.m' is extended at the LV node with a compliance in
19 % series with an inertance and a resistance. This group
20 % represents the part from the pump to the LV (feeding tube, LV champer)
    .
21 % The inlet flow profile is given by 'LPM-input-XYZ.txt' which is a file
22 % containing flow rate values ( $m^3/s$ ) of a normalized flow profile with
23 % a specific waveform.
24 %
25 % Changelog:
26 % removed hysteresis of valve opening (mitral and aortic) and reduced
27 % aortic valve resistance
28 % 04.01.17 using central-diff function for differentiation
29 %
30 %

```

```

31 % References:
32 % Stergiopoulos, 1999, "Total arterial inertance as the fourth element of
    the
33 %                               windkessel model"
34 %

35 %

36 clearvars except showplot N_puls;
37 close all; clc
38
39 % check input arguments
40
41 if nargin <1
42     showplot = 0;
43     N_puls = 20;
44 elseif nargin <2
45     N_puls = 20;
46 end
47
48 %
49 % PARaMETERS
50 %
51 g = 9.81;
52
53 % fluid
54 rho = 1050;
55 mu = 0.004;
56
57 % reference pressures
58 p_atm = 0; % ...0 if only interested in relative pressure
59 h_l = 0.21; % water level height in reference open reservoir
    (default is 0.4 m)
60 p_ref_l = p_atm + rho*g*h_l;
61
62 % resistance
63 R_a = 8e06; % [Pa s / m^3] Stergiopoulos (1999) 7464800
64 R_p = 1.5e08; % [Pa s / m^3] Stergiopoulos (1999) 105307000
65 RMV = 10*133.3/0.0002; % [Pa s / m^3]

```



```

66 R_AV = 1*133.3/0.0002;    % [Pa s / m^3]
67
68 d_f = 0.025; l_f = 0.2;
69 R_f = 128*mu*l_f/(d_f^4*pi);
70
71 % inertance
72 L_Ster = 7e05;            % [Pa s^2 / m^3] Stergiopoulos (1999) 679830
73
74 d_a = 0.025; l_a = 0.2;
75 L_a = rho*l_a/(d_a^4*pi); % accelerated fluid in aortic tube
76
77 L_f = rho*l_f/(d_f^4*pi); % accelerated fluid in feeding tube
78
79 % compliance
80 d_C = 0.114;
81 h_C = 0.12;
82 p_C_0 = 101325; V_C_0 = d_C^2/4*pi*h_C;
83 K = p_C_0/V_C_0;         % for air chamber
84
85 C_A = 1e 09;             % Stergiopoulos (1999) 9.1522880e 09
86 C_LV = 1e 10;
87 C_m = 1e 09;             % Compliance of LV membrane
88
89 % pulse periode
90 BPM = 60;
91 T = 60/BPM;
92
93 % aortic flow mean peak velocity
94 u_bar = 0.7;
95
96 % piston
97 d_p = 0.1;
98 mu_N = 50;               % Coulomb friction piston head [N]
99 m = 0.5;                 % Total mass of slide, support and piston [kg]
100
101 %
102 % Waveform
103 %
104 wf_data = importdata('LPM.input_phys_N100.txt');
105 wf = repmat(wf_data(1:end 1), 1, N_puls);
106

```

```

107 % time domain
108 time = linspace(0, T*N_puls, (length(wf_data) - 1)*N_puls);
109
110 % piston kinematics
111 v_p = d_a^2/d_p^2*u_bar*wf;
112 a_p = central_diff(v_p, time);
113
114 % flow rate
115 Q = v_p*d_p^2/4*pi;
116 Q_dot = central_diff(Q,time);
117 Q_ddot = central_diff(Q_dot,time);
118
119 %
120 % TIME INTEGRATION
121 %
122 %          pack arguments start
123 Arg.p_ref_1 = p_ref_1;
124 Arg.R_a = R_a;
125 Arg.R_p = R_p;
126 Arg.R_f = R_f;
127 Arg.RMV = RMV;
128 Arg.R_AV = R_AV;
129 Arg.L_a = L_a;
130 Arg.L_f = L_f;
131 Arg.K = K;
132 Arg.C_A = C_A;
133 Arg.C_LV = C_LV;
134 Arg.C_m = C_m;
135 %          pack arguments end
136
137 % initial state
138 p_0 = [p_ref_1, p_ref_1, 0, p_ref_1, 0, V_C_0, p_ref_1, p_ref_1];
139
140 t_span = [time(1), time(end)];
141 options = odeset('Mass',@(t, p) mass(t, p, Arg),...
142                 'MassSingular','no',...
143                 'RelTol',1e-5);
144
145 [T, P] = ode15s(@(t, p) rhs(t, p, Arg, time, Q, Q_ddot), t_span, p_0,
146                 options);

```

```

147 LVP = P(:,1);
148 pao = P(:,2);
149
150 %
151 % CARDIAC OUTPUT
152 %
153 Qa = zeros(length(T),1);
154 s1 = zeros(length(T),1);
155 s2 = zeros(length(T),1);
156 for i = 1:length(T)
157     t = T(i);
158     p = P(i,:);
159
160     Qa(i) = flow(t, p, Arg);
161
162     [R1, R2] = valves(t, p, Arg);
163
164     s1(i) = RMV/R1;
165     s2(i) = RAV/R2;
166 end
167
168 %
169 % LOAD ON LINEAR DRIVE
170 %
171
172 p_z = pchip(T, P(:,8), time) + Q*R_f;
173
174 % linear momentum
175 F_A = m*a_p + p_z*d_p^2/4*pi + muN*sign(v_p);
176
177 % torque
178 l_slide = 0.1;
179 M = l_slide*(p_z*d_p^2/4*pi + muN*sign(v_p));
180
181 %
182 % PLOTS
183 %
184
185 if showplot
186
187     hf1 = figure(1);

```

```

188     fs = 15;
189
190     subplot 311; hold on; lw = 1.5;
191     plot(T, P(:,1)/133.3, 'color', [0.9, 0.1, 0.1], 'linewidth', lw)
192     plot(T, P(:,2)/133.3, 'color', [0.5, 0.5, 0.5], 'linewidth', lw)
193     ylabel('pressure [mmHg]', 'fontsize', fs)
194     legend('p-{LV}', 'p-A', 'location', 'southeast')
195     grid on;
196
197     subplot 312; hold on;
198     plot(T, Qa*1e03, 'b', 'linewidth', lw)
199     plot(time, Q*1e03, 'b')
200     ylabel('flow_Rate [l/s]', 'fontsize', fs)
201     legend('Q-A', 'Q-p', 'location', 'southeast')
202     grid on;
203
204     subplot 313;
205     plot(T, s1, 'k', ...
206          T, s2, 'm')
207     xlabel('time_t [s]', 'fontsize', fs)
208     ylabel('valves', 'fontsize', fs)
209     ylim([0, 1.1])
210     legend('MV', 'AV', 'location', 'southeast')
211
212
213     hf2 = figure(2);
214     fs = 15;
215
216     subplot 311; hold on; lw = 1.5;
217     plot(T, P(:,1)/133.3, 'color', [0.9, 0.1, 0.1], 'linewidth', lw)
218     plot(T, P(:,2)/133.3, 'color', [0.5, 0.5, 0.5], 'linewidth', lw)
219     plot(T, P(:,8)/133.3, 'color', [0.7, 0.3, 0.1], 'linewidth', lw)
220     ylabel('pressure [mmHg]', 'fontsize', fs)
221     legend('p-{LV}', 'p-A', 'p-z', 'location', 'southeast')
222     grid on;
223
224     subplot 312; hold on;
225     plot(time, F_A, 'r', 'linewidth', lw)
226     ylabel('load [N]', 'fontsize', fs)
227     grid on;
228

```

```

229     subplot 313; hold on;
230     plot(time, M, 'r', 'linewidth', lw)
231     ylabel('load-[N]', 'fontsize', fs)
232     ylabel('time-[s]', 'fontsize', fs)
233     grid on;
234 end
235
236 % save
237 % orient landscape
238 % fillpage
239
240 % filename = 'Setup-2-flow-loop-output';
241 % print(hf1, filename, ' dpdf');
242 %
243 % filename = 'Setup-2-load-output';
244 % print(hf2, filename, ' dpdf');
245
246 end
247
248 %

249
250 function [f] = rhs(t, p, Arg, time, Q, Q_ddot)
251
252
253 %             unpack arguments start
254 p_ref_1 = Arg.p_ref_1;
255 L_a = Arg.L_a;
256 L_f = Arg.L_f;
257 K = Arg.K;
258 %             unpack arguments end
259
260 % inteR-polate input data
261 flow = pchip(time, Q, t);
262 flow_ddot = pchip(time, Q_ddot, t);
263
264 [R_MV_t, R_AV_t] = valves(t, p, Arg);
265
266 % define right hand side
267 f = zeros(8,1);

```

```

268
269 f(1) = flow + 1/R_MV_t*(p(1) - p_ref_1) + 1/R_AV_t*(p(1) - p(2));
270 f(2) = p(3);
271 f(3) = 1/L_a*(p(2) - p(4));
272 f(4) = p(5);
273 f(5) = 1/L_a*(p(2) - p(4)) - 2*p(6)^3/K^2*p(5)^2;
274 f(6) = p(6)^2/K*p(5);
275 f(7) = flow;
276 f(8) = flow_ddot;
277
278 end
279
280 %

281
282 function [M] = mass(t, p, Arg)
283
284 %           unpack arguments start
285 R_a = Arg.R_a;
286 R_p = Arg.R_p;
287 R_f = Arg.R_f;
288 L_f = Arg.L_f;
289 K = Arg.K;
290 C_A = Arg.C_A;
291 C_LV = Arg.C_LV;
292 C_m = Arg.C_m;
293 %           unpack arguments end
294
295 [R_MV_t, R_AV_t] = valves(t, p, Arg);
296
297 % mass matrix
298 M = [ C_LV, 0, 0, 0, 0, 0,
        0, 0;
299        0, 1, 0, 0, 0, 0,
        0, 0, 0, 0, 0, 0;
300        1/R_AV_t, (1/R_AV_t + 1/R_a), C_A, 1/R_a, 0, 0,
        0, 0;
301        0, 0, 0, 1, 0, 0,
        0, 0, 0, 0, 0, 0];

```

```

302         0,          1/R_a,      0,  (1/R_a + 1/R_p),  p(6)^2/K,
           0, 0, 0;
303         0,          0,      0,          0,          0, 1,
           0, 0;
304     C_m, 0, 0, 0, 0, 0, 0, C_m, 0;
305         0, 0, 0, 0, 0, 0, 1/L_f, 1/L_f];
306
307 end
308
309
310 %

```



```

311
312 function [R_MV_t, R_AV_t] = valves(t,p, Arg)
313
314 %      unpack arguments start
315 p_ref_1 = Arg.p_ref_1;
316 R_MV = Arg.R_MV;
317 R_AV = Arg.R_AV;
318 %      unpack arguments end
319
320
321 % limit pressure difference (opening / closure time of valves)
322 dp_hat_MV = 5*133.3;
323 dp_hat_AV = 5*133.3;
324
325 % valve resistance
326
327 % mitR_al valve
328 dp_MV = (p_ref_1 - p(1));
329
330 if dp_MV < 0;
331     T1 = 0;
332 % hysteresis commented out:
333 % elseif (0 <= dp_MV) && (dp_MV < dp_hat_MV) % smoothstep
334 %     T1 = 1/R_MV*(6*(dp_MV/dp_hat_MV)^5 ...
335 %         15*(dp_MV/dp_hat_MV)^4 ...
336 %         + 10*(dp_MV/dp_hat_MV)^3 );
337 %
338 else

```

```

339      T1 = 1/RMV;
340  end
341
342
343  % aortic valve
344  dp_AV = (p(1) - p(2));
345
346  if dp_AV < 0;
347      T2 = 0;
348  % hysteresis commented out:
349  % elseif (0 <= dp_AV) && (dp_AV < dp_hat_AV) % smoothstep
350  %      T2 = 1/RAV*(6*(dp_AV/dp_hat_AV)^5 ...
351  %          15*(dp_AV/dp_hat_AV)^4 ...
352  %          + 10*(dp_AV/dp_hat_AV)^3 );
353  else
354      T2 = 1/RAV;
355  end
356
357  R_MV_t = 1/T1;
358  R_AV_t = 1/T2;
359
360  end
361
362  %

```



```

363
364  function [Qa] = flow(t, p, Arg)
365
366  % aortic heart valve resistance
367  [R_MV_t, R_AV_t] = valves(t, p, Arg);
368
369  % aortic flow
370  Qa = (p(1) - p(2))/R_AV_t;
371
372  end
373
374  %

```



```

375

```



```

376 function [dxdt] = differentiate(x, t)
377
378 N = length(x);
379 dxdt = zeros(size(x));
380
381 for i = 1:N
382
383     if i == 1
384         dxdt(i) = (x(2) - x(1))/(t(2) - t(1));
385     elseif i == N
386         dxdt(i) = (x(N) - x(N-1))/(t(N) - t(N-1));
387     else
388         dxdt(i) = (x(i+1) - x(i-1))/(t(i+1) - t(i-1));
389     end
390 end
391
392
393 end

```

Listing 3: Input to the function linear'drive'load'setup'2

```
1  0.000000
2  0.014800
3  0.054400
4  0.111600
5  0.179200
6  0.250000
7  0.331520
8  0.428560
9  0.529840
10 0.624080
11 0.700000
12 0.754720
13 0.795760
14 0.827440
15 0.854080
16 0.880000
17 0.904720
18 0.925360
19 0.942640
20 0.957280
21 0.970000
22 0.980800
23 0.989200
24 0.995200
25 0.998800
26 1.000000
27 0.984800
28 0.942400
29 0.877600
30 0.795200
31 0.700000
32 0.568749
33 0.398248
34 0.223371
35 0.078997
36 0.000000
37 0.034252
38 0.067634
39 0.100133
40 0.131737
```

41	0.162432
42	0.192205
43	0.221044
44	0.248935
45	0.275866
46	0.301823
47	0.326794
48	0.350766
49	0.373726
50	0.395660
51	0.416557
52	0.436402
53	0.455184
54	0.472888
55	0.489503
56	0.505015
57	0.519412
58	0.532680
59	0.544806
60	0.555778
61	0.565582
62	0.574206
63	0.581637
64	0.587862
65	0.592867
66	0.596641
67	0.599169
68	0.600439
69	0.600177
70	0.596879
71	0.590484
72	0.581203
73	0.569244
74	0.554819
75	0.538137
76	0.519407
77	0.498841
78	0.476647
79	0.453037
80	0.428219
81	0.402404

82	0.375802
83	0.348622
84	0.321075
85	0.293370
86	0.265718
87	0.238328
88	0.211411
89	0.185176
90	0.159833
91	0.135593
92	0.112664
93	0.091258
94	0.071584
95	0.053852
96	0.038272
97	0.025054
98	0.014408
99	0.006543
100	0.001671
101	0.000000

Curriculum Vitae

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11/2011 – 05/2017 MD-PhD programme, Graduate School for Cellular and Biomedical Sciences, University of Bern, Switzerland
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2013 Poster presentation “Effects of intermittent coronary sinus occlusion on myocardial ischemia: role of coronary collateral function” at GCB Students' Symposium 2013”

2013 Poster presentation “Effects of Coronary Sinus Occlusion on Myocardial Ischemia: Role of Coronary Collateral Function” at the yearly conference of the European Society of Cardiology, Munich, Germany

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2014 Presentation “The Function of Natural Internal Mammary-to-Coronary Artery Bypasses and its Effect on Myocardial Ischemia” at the yearly conference by the Schweizerische Gesellschaft für Kardiologie

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2015 Poster presentation “Effect of Myocardial Ischemia on Inferolateral Early Repolarization”, annual meeting of the European Heart Rhythm Association, EHRA EUROPACE-CARDIOSTIM, Milano, Italy

2016 Poster presentation “Effect of Myocardial Ischemia on Inferolateral Early Repolarization”, yearly conference of the European Heart Rhythm Association, EHRA EUROPACE-CARDIOSTIM, Milano, Italy

2016 Presentation “Effect of Permanent Internal Mammary Artery Occlusion on Extracardiac Coronary Collateral Supply”, annual meeting of the Swiss Society of Cardiology

2016 Poster presentation “Impact of Acute Afterload Reduction by TAVI on the Human Coronary Circulation”, annual meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), EUROPCR, Paris, France

List of Publications

- [1] **Stoller, M** and Seiler, C. **2017**. Effect of Permanent Right Internal Mammary Artery Closure on Coronary Collateral Function and Myocardial Ischemia. *Circulation: Cardiovascular Interventions*;10:e004990.
- [2] **Stoller, M** and Seiler, C. **2017**. Reactive myocardial hyperaemia for functional assessment of coronary stenosis severity. *EuroIntervention*;13:e201–e209.
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- [4] **Stoller, M** and Seiler, C. **2016**. Intraindividual Variability and Association of Human Collateral Supply to Different Arterial Regions. *The American Journal of Cardiology*;117:685–690.
- [5] **Stoller, M**, Stoller, D, and Seiler, C. **2016**. Physical exercise and quantitative lower limb collateral function. *Open Heart*;3:e000355.
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- [16] Traupe, T, Ortmann, J, **Stoller, M**, Baumgartner, I, de Marchi, SF, and Seiler, C. **2013**. Direct Quantitative Assessment of the Peripheral Artery Collateral Circulation in Patients Undergoing Angiography. *Circulation*;128:737–744.

Declaration of Originality

Declaration of Originality

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Matriculation number: 03-135-407

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

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Place, date

Signature